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 ********** STN Columbus **********
FILE 'HOME' ENTERED AT 07:55:11 ON 25 AUG 2003
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E1       2   ALLAND CYNTHIA/AU
E2      93   ALLAND D/AU
E3      46 --> ALLAND DAVID/AU
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E5      54   ALLAND L/AU
E6      17   ALLAND LEILA/AU
E7       3   ALLAND M J/AU
E8       2   ALLAND STEPHEN W/AU
E9       7   ALLAND STEPHEN WILLIAM/AU
E10      1   ALLANDA J R/AU
E11      3   ALLANDA P/AU
E12      1   ALLANDE DARREN ANTHONY/AU

=> s e2-e3 and mycobact?
L1          131 ("ALLAND D"/AU OR "ALLAND DAVID"/AU) AND MYCOBACT?
=> dup rem l1
PROCESSING COMPLETED FOR L1
L2           37 DUP REM L1 (94 DUPLICATES REMOVED)
=> d bib ab 1-
YOU HAVE REQUESTED DATA FROM 37 ANSWERS - CONTINUE? Y/(N):y
 L2   ANSWER 1 OF 37  BIOSIS  COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
     DUPLICATE 1
AN   2003:350969  BIOSIS
DN   PREV200300350969
TI   Targeting tuberculosis and malaria through inhibition of enoyl reductase.
     Compound activity and structural data.
AU   Kuo, Mack R.; Morbidoni, Hector R.;   ***Alland, David***  ; Sneddon,
     Scott F.; Gourlie, Brian B.; Staveski, Mark M.; Leonard, Marina; Gregory,
     Jill S.; Janjigian, Andrew D.; Yee, Christopher; Musser, James M.;
     Kreiswirth, Barry; Iwamoto, Hiroyuki; Perozzo, Remo; Jacobs, William R.,
     Jr.; Sacchettini, James C. (1); Fidock, David A.
CS   (1) Dept. of Biochemistry and Biophysics, Texas A and M University,
     Biochemistry and Biophysics Bldg., Rm. 221, College Station, TX, 77843,
     USA: sacchett@tamu.edu USA
SO   Journal of Biological Chemistry, (June 6 2003) Vol. 278, No. 23, pp.
     20851-20859. print.
     ISSN: 0021-9258.
DT   Article
LA   English
AB   Tuberculosis and malaria together result in an estimated 5 million deaths
     annually. The spread of multi-drug resistance in the most pathogenic
     causative agents,   ***Mycobacterium***   tuberculosis and Plasmodium
     falciparum, underscores the need to identify active compounds with novel
     inhibitory properties. Although genetically unrelated, both organisms use
     a type II fatty-acid synthase system. Enoyl acyl carrier protein reductase
     (ENR), a key type II enzyme, has been repeatedly validated as an effective
     antimicrobial target. Using high throughput inhibitor screens with a
     combinatorial library, we have identified two novel classes of compounds
     with activity against the M. tuberculosis and P. falciparum enzyme
     (referred to as InhA and PfENR, respectively). The crystal structure of
     InhA complexed with NAD+ and one of the inhibitors was determined to
     elucidate the mode of binding. Structural analysis of InhA with the broad
     spectrum antimicrobial triclosan revealed a unique stoichiometry where the
     enzyme contained either a single triclosan molecule, in a configuration
     typical of other bacterial ENR:triclosan structures, or harbored two
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triclosan molecules bound to the active site. Significantly, these compounds do not require activation and are effective against wild-type and drug-resistant strains of M. tuberculosis and P. falciparum. Moreover, they provide broader chemical diversity and elucidate key elements of inhibitor binding to InhA for subsequent chemical optimization.

L2 ANSWER 2 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 2
AN 2003:281311 BIOSIS
DN PREV200300281311
TI Modeling bacterial evolution with comparative-genome-based marker systems: Application to ***Mycobacterium*** tuberculosis evolution and pathogenesis.
AU ***Alland, David (1)*** ; Whittam, Thomas S.; Murray, Megan B.; Cave, M. Donald; Hazbon, Manzour H.; Dix, Kim; Kokoris, Mark; Duesterhoeft, Andreas; Eisen, Jonathan A.; Fraser, Claire M.; Fleischmann, Robert D.
CS (1) Center for Emerging Pathogens, New Jersey Medical School, MSB A-920C, P.O. Box 1709, Newark, NJ, 07103, USA: allandda@umdnj.edu USA
SO Journal of Bacteriology, (June 2003, 2003) Vol. 185, No. 11, pp. 3392-3399. print.
ISSN: 0021-9193.
DT Article
LA English
AB The comparative-genomic sequencing of two ***Mycobacterium*** tuberculosis strains enabled us to identify single nucleotide polymorphism (SNP) markers for studies of evolution, pathogenesis, and epidemiology in clinical M. tuberculosis. Phylogenetic analysis using these "comparative-genome markers" (CGMs) produced a highly unusual phylogeny with a complete absence of secondary branches. To investigate CGM-based phylogenies, we devised computer models to simulate sequence evolution and calculate new phylogenies based on an SNP format. We found that CGMs represent a distinct class of phylogenetic markers that depend critically on the genetic distances between compared "reference strains." Properly distanced reference strains generate CGMs that accurately depict evolutionary relationships, distorted only by branch collapse. Improperly distanced reference strains generate CGMs that distort and reroot outgroups. Applying this understanding to the CGM-based phylogeny of M. tuberculosis, we found evidence to suggest that this species is highly clonal without detectable lateral gene exchange. We noted indications of evolutionary bottlenecks, including one at the level of the PHRI "C" strain previously associated with particular virulence characteristics. Our evidence also suggests that loss of IS6110 to fewer than seven elements per genome is uncommon. Finally, we present population-based evidence that KasA, an important component of mycolic acid biosynthesis, develops G312S polymorphisms under selective pressure.

L2 ANSWER 3 OF 37 USPATFULL on STN
AN 2002:272887 USPATFULL
TI IniB, iniA and iniC genes of ***mycobacteria*** and methods of use
IN ***Alland, David*** , Dobbs Ferry, NY, UNITED STATES
Bloom, Barry R., Hastings-on-Hudson, NY, UNITED STATES
Jacobs, William R., JR., City Island, NY, UNITED STATES
PI US 2002151008 A1 20021017
AI US 2001-918951 A1 20010731 (9)
RLI Continuation of Ser. No. US 1998-177349, filed on 23 Oct 1998, PATENTED
DT Utility
FS APPLICATION

LREP Elie H. Gendloff, Ph.D., Esq., AMSTER, ROTHSTEIN & EBENSTEIN, 90 Park Avenue, New York, NY, 10016
CLMN Number of Claims: 47
ECL Exemplary Claim: 1
DRWN 10 Drawing Page(s)
LN.CNT 935
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to the identification, cloning, sequencing and characterization of the iniB, iniA and iniC genes of ***mycobacteria*** which are induced by a broad class of antibiotics that act by inhibiting cell wall biosynthesis, including the first line antituberculosis agents, isoniazid and ethambutol. The present invention provides purified and isolated iniB, iniA, iniC and iniB promoter nucleic acids which may comprise the iniBAC operon, as well as mutated forms of these nucleic acids. The present invention also provides one or more single-stranded nucleic acid probes which specifically hybridize to the iniB, iniA, iniC and iniB promoter nucleic acids, and mixtures thereof, which may be formulated in kits, and used in the diagnosis of drug-resistant ***mycobacterial*** strain. The present invention also provides methods for the screening and identification of drugs effective against ***Mycobacterium*** tuberculosis using induction of the iniB promoter.

L2 ANSWER 4 OF 37 USPATFULL on STN
AN 2002:262205 USPATFULL
TI Non-competitive co-amplification methods
IN ***Alland, David*** , Dobbs Ferry, NY, United States
Kramer, Fred R., Riverdale, NY, United States
Piatek, Amy, Brookline, MA, United States
Tyagi, Sanjay, New York, NY, United States
Vet, Jacqueline, Malden, NETHERLANDS
PA The Public Health Research Institute of the City of New York, Newark, NJ, United States (U.S. corporation)
PI US 6461817 B1 20021008
WO 9913113 19990318
AI US 2000-508343 20001020 (9)
WO 1998-US19182 19980911
20001020 PCT 371 date
PRAI US 1997-58729P 19970912 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Whisenant, Ethan C.
LREP Fish & Richardson PC
CLMN Number of Claims: 16
ECL Exemplary Claim: 1
DRWN 4 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 730
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Non-competitive, quantitative amplification assay methods, including assays employing amplification by the polymerase chain reaction (PCR) process, for accurately measuring levels of target nucleic acid and sequences in samples and for ascertaining the relative amounts of cross-hybridizing alleles and mutants.

L2 ANSWER 5 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 3
AN 2002:517542 BIOSIS

DN PREV200200517542
TI Whole-genome comparison of ***Mycobacterium*** tuberculosis clinical and laboratory strains.
AU Fleischmann, R. D. (1); ***Alland, D.*** ; Eisen, J. A.; Carpenter, L.; White, O.; Peterson, J.; DeBoy, R.; Dodson, R.; Gwinn, M.; Haft, D.; Hickey, E.; Kolonay, J. F.; Nelson, W. C.; Umayam, L. A.; Ermolaeva, M.; Salzberg, S. L.; Delcher, A.; Utterback, T.; Weidman, J.; Khouri, H.; Gill, J.; Mikula, A.; Bishai, W.; Jacobs, W. R., Jr.; Venter, J. C.; Fraser, C. M.
CS (1) Institute for Genomic Research, 9712 Medical Center Dr., Rockville, MD, 20850: rdfleisc@tigr.org USA
SO Journal of Bacteriology, (October, 2002) Vol. 184, No. 19, pp. 5479-5490. http://intl-jb.asm.org/. print.
ISSN: 0021-9193.
DT Article
LA English
AB Virulence and immunity are poorly understood in ***Mycobacterium*** tuberculosis. We sequenced the complete genome of the M. tuberculosis clinical strain CDC1551 and performed a whole-genome comparison with the laboratory strain H37Rv in order to identify polymorphic sequences with potential relevance to disease pathogenesis, immunity, and evolution. We found large-sequence and single-nucleotide polymorphisms in numerous genes. Polymorphic loci included a phospholipase C, a membrane lipoprotein, members of an adenylate cyclase gene family, and members of the PE/PPE gene family, some of which have been implicated in virulence or the host immune response. Several gene families, including the PE/PPE gene family, also had significantly higher synonymous and nonsynonymous substitution frequencies compared to the genome as a whole. We tested a large sample of M. tuberculosis clinical isolates for a subset of the large-sequence and single-nucleotide polymorphisms and found widespread genetic variability at many of these loci. We performed phylogenetic and epidemiological analysis to investigate the evolutionary relationships among isolates and the origins of specific polymorphic loci. A number of these polymorphisms appear to have occurred multiple times as independent events, suggesting that these changes may be under selective pressure. Together, these results demonstrate that polymorphisms among M. tuberculosis strains are more extensive than initially anticipated, and genetic variation may have an important role in disease pathogenesis and immunity.

L2 ANSWER 6 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 4
AN 2002:221238 BIOSIS
DN PREV200200221238
TI Methodological problems in the molecular epidemiology of tuberculosis.
AU Murray, Megan (1); ***Alland, David***
CS (1) Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA, 02115: mmurray@hsph.harvard.edu USA
SO American Journal of Epidemiology, (March 15, 2002) Vol. 155, No. 6, pp. 565-571. http://www.aje.oupjournals.org. print.
ISSN: 0002-9262.
DT General Review
LA English
AB In systematic studies of the molecular epidemiology of tuberculosis, DNA fingerprinting is used to estimate the fraction of incident cases attributable to recent transmission of ***Mycobacterium*** tuberculosis rather than reactivation disease and to identify risk factors

for recent transmission. This approach is based on the premise that tuberculosis cases that share a DNA fingerprint are epidemiologically related while cases in which fingerprints are unique are due to remote infection that has reactivated. In this paper, the authors review the objectives and design of molecular epidemiologic studies of tuberculosis, describe current analytical approaches, and consider the impact of these different approaches on study results. Using data from a previously published investigation of the epidemiology of tuberculosis conducted from 1990 to 1993 among tuberculosis patients in New York City, New York, the authors show how selecting different measures of disease frequency, comparison groups, and sampling strategies may impact the results and interpretability of the study. They demonstrate ways to conduct sensitivity analyses of estimated results and suggest strategies that may improve the usefulness of this approach to studying tuberculosis.

L2 ANSWER 7 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 5
AN 2002:577335 BIOSIS
DN PREV200200577335
TI Overexpression of inhA, but not kasA, confers resistance to isoniazid and ethionamide in ***Mycobacterium*** smegmatis, M. bovis BCG and M. tuberculosis.
AU Larsen, Michelle H.; Vilcheze, Catherine; Kremer, Laurent; Besra, Gurdyal S.; Parsons, Linda; Salfinger, Max; Heifets, Leonid; Hazbon, Manzour H.; ***Alland, David*** ; Sacchettini, James C.; Jacobs, William R., Jr. (1)
CS (1) Department of Microbiology and Immunology, Howard Hughes Medical Institute, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY, 10461: jacobsw@hhmi.org.edu USA
SO Molecular Microbiology, (October, 2002) Vol. 46, No. 2, pp. 453-466. http://www.mol.micro.com. print.
ISSN: 0950-382X.
DT Article
LA English
AB The inhA and kasA genes of ***Mycobacterium*** tuberculosis have each been proposed to encode the primary target of the antibiotic isoniazid (INH). Previous studies investigating whether overexpressed inhA or kasA could confer resistance to INH yielded disparate results. In this work, multicopy plasmids expressing either inhA or kasA genes were transformed into M. smegmatis, M. bovis BCG and three different M. tuberculosis strains. The resulting transformants, as well as previously published M. tuberculosis strains with multicopy inhA or kasAB plasmids, were tested for their resistance to INH, ethionamide (ETH) or thiolactomycin (TLM). ***Mycobacteria*** containing inhA plasmids uniformly exhibited 20-fold or greater increased resistance to INH and 10-fold or greater increased resistance to ETH. In contrast, the kasA plasmid conferred no increased resistance to INH or ETH in any of the five strains, but it did confer resistance to thiolactomycin, a known KasA inhibitor. INH is known to increase the expression of kasA in INH-susceptible M. tuberculosis strains. Using molecular beacons, quantified inhA and kasA mRNA levels showed that increased inhA mRNA levels correlated with INH resistance, whereas kasA mRNA levels did not. In summary, analysis of strains harbouring inhA or kasA plasmids yielded the same conclusion: overexpressed inhA, but not kasA, confers INH and ETH resistance to M. smegmatis, M. bovis BCG and M. tuberculosis. Therefore, InhA is the primary target of action of INH and ETH in all three species.

L2 ANSWER 8 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

DUPLICATE 6
AN 2001:455186 BIOSIS
DN PREV200100455186
TI IniB, iniA and iniC genes of ***mycobacteria*** and methods of use.
AU ***Alland, David*** ; Bloom, Barry R.; Jacobs, William R., Jr.
CS Dobbs Ferry, NY USA
ASSIGNEE: Albert Einstein College of Medicine of Yeshiva University
PI US 6268201 July 31, 2001
SO Official Gazette of the United States Patent and Trademark Office Patents, (July 31, 2001) Vol. 1248, No. 5, pp. No Pagination. e-file.
ISSN: 0098-1133.
DT Patent
LA English
AB This invention relates to the identification, cloning, sequencing and characterization of the iniB, iniA and iniC genes of ***mycobacteria*** which are induced by a broad class of antibiotics that act by inhibiting cell wall biosynthesis, including the first line antituberculosis agents, isoniazid and ethambutol. The present invention provides purified and isolated iniB, iniA, iniC and iniB promoter nucleic acids which may comprise the iniBAC operon, as well as mutated forms of these nucleic acids. The present invention also provides one or more single-stranded nucleic acid probes which specifically hybridize to the iniB, iniA, iniC and iniB promoter nucleic acids, and mixtures thereof, which may be formulated in kits, and used in the diagnosis of drug-resistant ***mycobacterial*** strain. The present invention also provides methods for the screening and identification of drugs effective against ***Mycobacterium*** tuberculosis using induction of the iniB promoter.

L2 ANSWER 9 OF 37 CAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 7
AN 2001:886796 CAPLUS
DN 136:32643
TI Method of identification of differentially expressed mRNA using customized amplification libraries (CAL)
IN ***Alland, David*** ; Bloom, Barry R.; Kramnik, Igor
PA USA
SO U.S. Pat. Appl. Publ., 19 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2001049094	A1	20011206	US 1998-178098	19981023
	US 6458566	B2	20021001		
PRAI	US 1998-178098		19981023		

AB The method provided by the present invention sets forth a novel combination of methods and principles which allows for the rapid and accurate isolation and identification of a large no. of differentially expressed mRNAs. The inventors have termed the novel approach for studying differences in mRNA expression "differential expression using customized amplification libraries" (DECAL), that permits global comparisons of bacterial gene expression under varied growth conditions without a specific requirement for DNA arrays. The key feature of DECAL technol. is the ability to amplify by PCR a complex mixt. of expressed genes in a reproducible and representative manner without the confounding effects of rRNA or any other highly expressed gene product. The inventors have found that three steps are essential for this process: (i) removal of

abundant sequences--in this case rRNA sequences; (ii) redn. in the complexity of the sequences and conversion of all cDNA sequences into fragments of similar size; and (iii) selecting sequences that amplify efficiently. DECAL accomplishes this by creating a customized amplification library (CAL) of genomic sequences that has been manipulated for optimal performance during PCR amplification. Instead of amplifying total cDNA sequences, cDNA is hybridized to an excess of CAL, nonhybridizing CAL sequences are removed and the remaining CAL sequences are amplified without altering their proportion representation. The inventors have herein demonstrated the applicability of the DECAL system to the study of ***Mycobacterium*** tuberculosis gene expression in response to the antibiotic, isoniazid.

L2 ANSWER 10 OF 37 CAPLUS .COPYRIGHT 2003 ACS on STN
AN 2001:320153 CAPLUS
DN 134:348924
TI Assays for short sequence variants using sloppy molecular beacon probes and its application
IN Tyagi, Sanjay; Kramer, Fred R.; ***Alland, David***
PA Public Health Research Institute of the City of New York, Inc., USA
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001031062	A1	20010503	WO 2000-US28515	20001013
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 1230387	A1	20020814	EP 2000-970925	20001013
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
	JP 2003518924	T2	20030617	JP 2001-533197	20001013
PRAI	US 1999-161096P	P	19991022		
	WO 2000-US28515	W	20001013		

AB The invention provides assays that can detect multiple genetic variants of a gene (e.g., a ***mycobacterial*** gene) in a sample using a pool (e.g., 2,3,4, or more) of oligonucleotide hybridization probes. The variants to be detected can be variants of eukaryotic genes, including a mammalian allele or somatic mutant assocd. with a metabolic disease (such as an allele of the globin gene), or oncogene (such as ras oncogene). Alternatively, the gene can be a microbial (e.g., bacterial, viral, or parasitic) allele. An example is described utilizing four sloppy mol. beacon probes to identify different ***mycobacterial*** species by detecting the sequences of a hypervariable species-specific region of the ***mycobacterial*** 16S rRNA gene. The invention also includes kits of reagents contg. combinations of the said probes for detecting any of the said genetic variants in a sample. The method can be used in metabolic disease diagnosis or species identification.

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 11 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 8
AN 2002:55131 BIOSIS
DN PREV200200055131
TI The inducible nitric oxide synthase locus confers protection against aerogenic challenge of both clinical and laboratory strains of ***Mycobacterium*** tuberculosis in mice.
AU Scanga, Charles A.; Mohan, Vellore P.; Tanaka, Kathryn; ***Alland,*** *** David*** ; Flynn, JoAnne L.; Chan, John (1)
CS (1) Departments of Medicine, Microbiology, and Immunology, Albert Einstein College of Medicine, 1300 Morris Park Ave., Bronx, NY, 10461: jchan@aecom.yu.edu USA
SO Infection and Immunity, (December, 2001) Vol. 69, No. 12, pp. 7711-7717. print.
ISSN: 0019-9567.
DT Article
LA English
AB Murine macrophages effect potent antimycobacterial function via the production of nitric oxide by the inducible isoform of the enzyme nitric oxide synthase (NOS2). The protective role of reactive nitrogen intermediates (RNI) against ***Mycobacterium*** tuberculosis infection has been well established in various murine experimental tuberculosis models using laboratory strains of the tubercle bacillus to establish infection by the intravenous route. However, important questions remain about the in vivo importance of RNI in host defense against M. tuberculosis. There is some evidence that RNI play a lesser role following aerogenic, rather than intravenous, M. tuberculosis infection of mice. Furthermore, in vitro studies have demonstrated that different strains of M. tuberculosis, including clinical isolates, vary widely in their susceptibility to the antimycobacterial effects of RNI. Thus, we sought to test rigorously the protective role of RNI against infection with recent clinical isolates of M. tuberculosis following both aerogenic and intravenous challenges. Three recently isolated and unique M. tuberculosis strains were used to infect both wild-type (wt) C57BL/6 and NOS2 gene-disrupted mice. Regardless of the route of infection, NOS2-/- mice were much more susceptible than wt mice to any of the clinical isolates or to either the Erdman or H37Rv laboratory strain of M. tuberculosis. ***Mycobacteria*** replicated to much higher levels in the organs of NOS2-/- mice than in those of wt mice. Although the clinical isolates all exhibited enhanced virulence in NOS2-/- mice, they displayed distinct growth rates in vivo. The present study has provided results indicating that RNI are required for the control of murine tuberculous infection caused by both laboratory and clinical strains of M. tuberculosis. This protective role of RNI is essential for the control of infection established by either intravenous or aerogenic challenge.

L2 ANSWER 12 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 9
AN 2002:7810 BIOSIS
DN PREV200200007810
TI Detection of rifampin resistance in ***Mycobacterium*** tuberculosis in a single tube with molecular beacons.
AU El-Hajj, Hiyam H.; Marras, Salvatore A. E.; Tyagi, Sanjay; Kramer, Fred Russell (1); ***Alland, David***

CS (1) Department of Molecular Genetics, Public Health Research Institute, 455 First Ave., New York, NY, 10016: kramer@phri.nyu.edu USA
SO Journal of Clinical Microbiology, (November, 2001) Vol. 39, No. 11, pp. 4131-4137. print.
ISSN: 0095-1137.
DT Article
LA English
AB Current clinical assays for determining antibiotic susceptibility in ***Mycobacterium*** tuberculosis require many weeks to complete due to the slow growth of the bacilli. Here we demonstrate an extremely sensitive single-tube PCR assay that takes less than 3 h and reliably identifies rifampin-resistant M. tuberculosis in DNA extracted directly from sputum. Ninety-five percent of mutations associated with rifampin resistance occur in an 81-bp core region of the bacterial RNA polymerase gene, rpoB. All mutations that occur within this region result in rifampin resistance. The assay uses novel nucleic acid hybridization probes called molecular beacons. Five different probes are used in the same reaction, each perfectly complementary to a different target sequence within the rpoB gene of rifampin-susceptible bacilli and each labeled with a differently colored fluorophore. Together, their target sequences encompass the entire core region. The generation of all five fluorescent colors during PCR amplification indicates that rifampin-susceptible M. tuberculosis is present. The presence of any mutation in the core region prevents the binding of one of the molecular beacons, resulting in the absence of one of the five fluorescent colors. When 148 M. tuberculosis clinical isolates of known susceptibility to rifampin were tested, mutations associated with rifampin resistance were detected in 63 of the 65 rifampin-resistant isolates, and no mutations were found in any of the 83 rifampin-susceptible isolates. When DNA extracted directly from the sputum of 11 patients infected with rifampin-resistant tuberculosis was tested, mutations were detected in all of the samples. The use of this rapid assay should enable early detection and treatment of drug-resistant tuberculosis in clinical settings.

L2 ANSWER 13 OF 37 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
AN 2001:761335 SCISEARCH
GA The Genuine Article (R) Number: 474GU
TI Rapid and sensitive detection of ***Mycobacterium*** DNA using cepheid SmartCycler (R) and tube lysis system
AU Jones M (Reprint); ***Alland D*** ; Marras S; El-Hajj H; Taylor M T; McMillan W
CS Cepheid Inc, Sunnyvale, CA 94089 USA; Montefiore Med Ctr, Bronx, NY 10467 USA; Publ Hlth Res Inst, New York, NY 10016 USA
CYA USA
SO CLINICAL CHEMISTRY, (OCT 2001) Vol. 47, No. 10, pp. 1917-1918.
Publisher: AMER ASSOC CLINICAL CHEMISTRY, 2101 L STREET NW, SUITE 202, WASHINGTON, DC 20037-1526 USA.
ISSN: 0009-9147.
DT Conference; Journal
LA English
REC Reference Count: 0

L2 ANSWER 14 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 10
AN 2000:310701 BIOSIS
DN PREV200000310701
TI Thiolactomycin and related analogues as novel anti- ***mycobacterial***

agents targeting KasA and KasB condensing enzymes in ***Mycobacterium*** tuberculosis.

AU Kremer, Laurent; Douglas, James D.; Baulard, Alain R.; Morehouse, Caroline; Guy, Mark R.; ***Alland, David*** ; Dover, Lynn G.; Lakey, Jeremy H.; Jacobs, William R., Jr.; Brennan, Patrick J.; Minnikin, David E.; Besra, Gurdyal S. (1)

CS (1) Department of Microbiology and Immunology, University of Newcastle upon Tyne, Newcastle upon Tyne, NE2 4HH UK

SO Journal of Biological Chemistry, (June 2, 2000) Vol. 275, No. 22, pp. 16857-16864. print.
ISSN: 0021-9258.

DT Article

LA English

SL English

AB Prevention efforts and control of tuberculosis are seriously hampered by the appearance of multidrug-resistant strains of ***Mycobacterium*** tuberculosis, dictating new approaches to the treatment of the disease. Thiolactomycin (TLM) is a unique thiolactone that has been shown to exhibit anti- ***mycobacterial*** activity by specifically inhibiting fatty acid and mycolic acid biosynthesis. In this study, we present evidence that TLM targets two beta-ketoacyl-acyl-carrier protein synthases, KasA and KasB, consistent with the fact that both enzymes belong to the fatty-acid synthase type II system involved in fatty acid and mycolic acid biosynthesis. Overexpression of KasA, KasB, and KasAB in ***Mycobacterium*** bovis BCG increased in vivo and in vitro resistance against TLM. In addition, a multidrug-resistant clinical isolate was also found to be highly sensitive to TLM, indicating promise in counteracting multidrug-resistant strains of M. tuberculosis. The design and synthesis of several TLM derivatives have led to compounds more potent both in vitro against fatty acid and mycolic acid biosynthesis and in vivo against M. tuberculosis. Finally, a three-dimensional structural model of KasA has also been generated to improve understanding of the catalytic site of ***mycobacterial*** Kas proteins and to provide a more rational approach to the design of new drugs.

L2 ANSWER 15 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 11

AN 2000:179354 BIOSIS

DN PREV200000179354

TI Characterization of the ***Mycobacterium*** tuberculosis iniBAC promoter, a promoter that responds to cell wall biosynthesis inhibition.

AU ***Alland, David (1)*** ; Steyn, Andries J.; Weisbrod, Torin; Aldrich, Kate; Jacobs, William R., Jr.

CS (1) Division of Infectious Diseases, Montefiore Medical Center, 111 East 210th St., Centennial Building 4th floor, Bronx, NY, 10467 USA

SO Journal of Bacteriology, (April, 2000) Vol. 182, No. 7, pp. 1802-1811.
ISSN: 0021-9193.

DT Article

LA English

SL English

AB The cell wall provides an attractive target for antibiotics against ***Mycobacterium*** tuberculosis. Agents such as isoniazid and ethambutol that work by inhibiting cell wall biosynthesis are among the most highly effective antibiotics against this pathogen. Although considerable progress has been made identifying the targets for cell wall active antibiotics, little is known about the intracellular mechanisms

that are activated as a consequence of cell wall injury. These mechanisms are likely to have an important role in growth regulation and in the induction of cell death by antibiotics. We previously discovered three isoniazid-induced genes (iniB, iniA, and iniC) organized in tandem on the M. tuberculosis genome. Here, we investigate the unique features of the putative iniBAC promoter. This promoter was specifically induced by a broad range of inhibitors of cell wall biosynthesis but was not inducible by other conditions that are toxic to ***mycobacteria*** via other mechanisms. Induction required inhibitory concentrations of antibiotics and could be detected only in actively growing cells. Analysis of the iniBAC promoter sequence revealed both a regulatory element upstream and a potential repressor binding region downstream of the transcriptional start site. The induction phenotype and structure of the iniBAC promoter suggest that a complex intracellular response occurs when cell wall biosynthesis is inhibited in M. tuberculosis and other ***mycobacteria*** .

L2 ANSWER 16 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 12
AN 2000:93464 BIOSIS
DN PREV200000093464
TI Genotypic analysis of ***Mycobacterium*** tuberculosis in two distinct populations using molecular beacons: Implications for rapid susceptibility testing.
AU Piatek, Amy S.; Telenti, Amalio; Murray, Megan R.; El-Hajj, Hiyam; Jacobs, William R., Jr.; Kramer, Fred Russell; ***Alland, David (1)***
CS (1) Division of Infectious Diseases, Department of Medicine, Montefiore Medical Center, 111 East 210th St., Bronx, NY, 10467-2490 USA
SO Antimicrobial Agents and Chemotherapy, (Jan., 2000) Vol. 44, No. 1, pp. 103-110.
ISSN: 0066-4804.
DT Article
LA English
SL English
AB Past genotypic studies of ***Mycobacterium*** tuberculosis may have incorrectly estimated the importance of specific drug resistance mutations due to a number of sampling biases including an overrepresentation of multidrug-resistant (MDR) isolates. An accurate assessment of resistance mutations is crucial for understanding basic resistance mechanisms and designing genotypic drug resistance assays. We developed a rapid closed-tube PCR assay using fluorogenic reporter molecules called molecular beacons to detect reportedly common M. tuberculosis mutations associated with resistance to isoniazid and rifampin. The assay was used in a comparative genotypic investigation of two different study populations to determine whether these known mutations account for most cases of clinical drug resistance. We analyzed samples from a reference laboratory in Madrid, Spain, which receives an overrepresentation of MDR isolates similar to prior studies and from a community medical center in New York where almost all of the resistant isolates and an equal number of susceptible controls were available. The ability of the molecular beacon assay to predict resistance to isoniazid and rifampin was also assessed. The overall sensitivity and specificity of the assay for isoniazid resistance were 85 and 100%, respectively, and those for rifampin resistance were 98 and 100%, respectively. Rifampin resistance mutations were detected equally well in isolates from both study populations; however, isoniazid resistance mutations were detected in 94% of the isolates from Madrid but in only 76% of the isolates from New York (P = 0.02). In New York, isoniazid resistance mutations were significantly more

common in the MDR isolates (94%) than in single-drug-resistant isolates (44%; P < 0.001). No association between previously described mutations in the kasA gene and isoniazid resistance was found. The first mutations that cause isoniazid resistance may often occur in sequences that have not been commonly associated with isoniazid resistance, possibly in other as yet uncharacterized genes. The molecular beacon assay was simple, rapid, and highly sensitive for the detection of rifampin-resistant M. tuberculosis isolates and for the detection of isoniazid resistance in MDR isolates.

L2 ANSWER 17 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:378898 BIOSIS
DN PREV200000378898
TI Identification and characterization of a ***Mycobacterium*** tuberculosis promoter that is induced by a broad range of antibiotics that inhibit cell wall biosynthesis.
AU ***Alland, David (1)*** ; Cerny, Rosaria (1); Steyn, Adrie J.; Weisbrod, Torin; Bloom, Barry R.; Jacobs, William R., Jr.
CS (1) Division of Infectious Diseases, Montefiore Medical Center, Bronx, NY, 10467 USA
SO Tubercle and Lung Disease, (2000) Vol. 80, No. 2, pp. 85-86. print.
Meeting Info.: Tuberculosis-Leprosy Panel's 34th Annual Research Conference on the US-Japan Cooperative Medical Science Program San Francisco, California, USA June 27-30, 1999
ISSN: 0962-8479.
DT Conference
LA English
SL English

L2 ANSWER 18 OF 37 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
DUPLICATE 13
AN 2000082135 EMBASE
TI Molecular determinants of drug resistance in tuberculosis.
AU Riska P.F.; Jacobs W.R. Jr.; ***Alland D.***
CS D. Alland, Montefiore Medical Center, 11 E 20th Street, Bronx, NY 10046, United States. dalland404@aol.com
SO International Journal of Tuberculosis and Lung Disease, (2000) 4/2 SUPPL. 1 (S4-S10).
Refs: 73
ISSN: 1027-3719 CODEN: IJTDFO
CY France
DT Journal; Conference Article
FS 004 Microbiology
015 Chest Diseases, Thoracic Surgery and Tuberculosis
037 Drug Literature Index
LA English
SL English
AB Rapid detection of drug-resistant tuberculosis (TB) has become increasingly important in the era of pandemic human immunodeficiency virus infection and antibiotic resistance. The identification of the molecular correlates of antibiotic resistance in ***Mycobacterium*** tuberculosis have engendered the development of DNA-based assays for the identification of drug-resistant TB. This review summarizes the recent discoveries concerning resistance to isoniazid, rifampin, pyrazinamide, ethambutol, streptomycin, amikacin, kanamycin and the quinolones.

L2 ANSWER 19 OF 37 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1999:194298 CAPLUS

DN 130:219130
TI Non-competitive co-amplification methods for determination of target nucleic acid sequences
IN Kramer, Fred R.; Tyagi, Sanjay; ***Alland, David*** ; Vet, Jacqueline; Piatek, Amy
PA The Public Health Research Institute of the City of New York, Inc., USA
SO PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9913113	A1	19990318	WO 1998-US19182	19980911
	W: AU, CA, JP, US				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2303414	AA	19990318	CA 1998-2303414	19980911
	AU 9894846	A1	19990329	AU 1998-94846	19980911
	AU 743011	B2	20020117		
	EP 1012344	A1	20000628	EP 1998-948229	19980911
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, IE, FI				
	JP 2001515734	T2	20010925	JP 2000-510898	19980911
	US 6461817	B1	20021008	US 2000-508343	20001020
PRAI	US 1997-58729P	P	19970912		
	WO 1998-US19182	W	19980911		

AB The invention provides non-competitive, quant. amplification assays, including PCR assays useful in accurately measuring levels of target nucleic acid sequences in samples and of ascertaining the relative amts. of cross-hybridizing alleles and mutants. Two or more different sequences that cross-hybridize, as during the annealing step of a PCR reaction, can be co-amplified using a single set of primers. "Cross-hybridize" means that the amplicons of each sequence hybridize not only to themselves but also to amplicons of the other sequences; for such sequences, the amplifications of the sequences are linked and follow the same reaction kinetics and act as a single amplicon. This is referred to as non-competitive amplification. An aspect of this invention is nucleic acid hybridization assays that do not require post-amplification manipulation, that include at least 2 sequence which are subject to the same reaction kinetics, and that include homogeneous detection utilizing interactively dual-labeled hybridization probes. The precision of these quant., homogeneous PCR assays is significantly improved over the 30% variability of real-time PCR. The method is exemplified by PCR amplification kinetics of a ***Mycobacterium*** tuberculosis strain M235 rpoB gene sequence present at different concns. relative to those of an rpoB gene from M. tuberculosis J24.
RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 20 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 14
AN 1999:522117 BIOSIS
DN PREV199900522117
TI Molecular epidemiologic evaluation of transmissibility and virulence of ***Mycobacterium*** tuberculosis.
AU Rhee, Jeanne T.; Piatek, Amy S.; Small, Peter M. (1); Harris, Lisa M.; Chaparro, Sandra V.; Kramer, Fred Russell; ***Alland, David***

CS (1) Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine, 300 Pasteur Drive, Room S-143, Stanford, CA, 94305 USA
SO Journal of Clinical Microbiology, (June, 1999) Vol. 37, No. 6, pp. 1764-1770.
ISSN: 0095-1137.
DT Article
LA English
SL English
AB Discovery of genotypic markers associated with increased transmissibility in ***Mycobacterium*** tuberculosis would represent an important step in advancing ***mycobacterial*** virulence studies. M. tuberculosis strains may be classified into one of three genotypes on the basis of the presence of specific nucleotide substitutions in codon 463 of the katG gene (katG-463) and codon 95 of the gyrA gene (gyrA-95). It has previously been reported that two of these three genotypes are associated with increased IS6110-based clustering, a potential proxy of virulence. We designed a case-control analysis of U.S.-born patients with tuberculosis in San Francisco, Calif., between 1991 and 1997 to investigate associations between katG-463 and gyrA-95 genotypes and epidemiologically determined measures of strain-specific infectivity and pathogenicity and IS6110-based clustering status. We used a new class of molecular probes called molecular beacons to genotype the isolates rapidly. Infectivity was defined as the propensity of isolates to cause tuberculin skin test conversions among named contacts, and pathogenicity was defined as their propensity to cause active disease among named contacts. The molecular beacon assay was a simple and reproducible method for the detection of known single nucleotide polymorphisms in large numbers of clinical M. tuberculosis isolates. The results showed that no genotype of the katG-463 and gyrA-95-based classification system was associated with increased infectivity and pathogenicity or with increased IS6110-based clustering in San Francisco during the study period. We speculate that molecular epidemiologic studies investigating clinically relevant outcomes may contribute to the knowledge of the significance of laboratory-derived virulence factors in the propagation of tuberculosis in human communities.

L2 ANSWER 21 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 15
AN 1999:4927 BIOSIS
DN PREV199900004927
TI Identification of differentially expressed mRNA in prokaryotic organisms by customized amplification libraries (DECAL): The effect of isoniazid on gene expression in ***Mycobacterium*** tuberculosis.
AU ***Alland, David (1)*** ; Kramnik, Igor; Weisbrod, Torin R.; Otsubo, Lisa; Cerny, Rosaria; Miller, Lincoln P.; Jacobs, William R., Jr.; Bloom, Barry R.
CS (1) Div. Infectious Disease, Montefiore Medical Cent., 111 East 210th St., Bronx, NY 10467 USA
SO Proceedings of the National Academy of Sciences of the United States of America, (Oct. 27, 1998) Vol. 95, No. 22, pp. 13227-13232.
ISSN: 0027-8424.
DT Article
LA English
AB Understanding the effects of the external environment on bacterial gene expression can provide valuable insights into an array of cellular mechanisms including pathogenesis, drug resistance, and, in the case of ***Mycobacterium*** tuberculosis, latency. Because of the absence of

poly(A)+ mRNA in prokaryotic organisms, studies of differential gene expression currently must be performed either with large amounts of total RNA or rely on amplification techniques that can alter the proportional representation of individual mRNA sequences. We have developed an approach to study differences in bacterial mRNA expression that enables amplification by the PCR of a complex mixture of cDNA sequences in a reproducible manner that obviates the confounding effects of selected highly expressed sequences, e.g., ribosomal RNA. Differential expression using customized amplification libraries (DECAL) uses a library of amplifiable genomic sequences to convert total cellular RNA into an amplified probe for gene expression screens. DECAL can detect 4-fold differences in the mRNA levels of rare sequences and can be performed on as little as 10 ng of total RNA. DECAL was used to investigate the in vitro effect of the antibiotic isoniazid on M. tuberculosis, and three previously uncharacterized isoniazid-induced genes, iniA, iniB, and iniC, were identified. The iniB gene has homology to cell wall proteins, and iniA contains a phosphopantetheine attachment site motif suggestive of an acyl carrier protein. The iniA gene is also induced by the antibiotic ethambutol, an agent that inhibits cell wall biosynthesis by a mechanism that is distinct from isoniazid. The DECAL method offers a powerful new tool for the study of differential gene expression.

L2 ANSWER 22 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 16
AN 1998:271009 BIOSIS
DN PREV199800271009
TI Simultaneous genotyping and species identification using hybridization pattern recognition analysis of generic ***Mycobacterium*** DNA arrays.
AU Gingeras, Thomas R. (1); Ghandour, Ghassan; Wang, Eugene; Berno, Anthony; Small, Peter M.; Drobniewski, Francis; ***Alland, David*** ; Desmond, Edward; Holodny, Mark; Drenkow, Jorg
CS (1) Affymetrix, Santa Clara, CA 95051 USA
SO Genome Research, (May, 1998) Vol. 8, No. 5, pp. 435-448.
ISSN: 1088-9051.
DT Article
LA English
AB High-density oligonucleotide arrays can be used to rapidly examine large amounts of DNA sequence in a high throughput manner. An array designed to determine the specific nucleotide sequence of 705 bp of the rpoB gene of ***Mycobacterium*** tuberculosis accurately detected rifampin resistance
associated with mutations of 44 clinical isolates of M. tuberculosis. The nucleotide sequence diversity in 121 ***Mycobacterial*** isolates (comprised of 10 species) was examined by both conventional dideoxynucleotide sequencing of the rpoB and 16S genes and by analysis of the rpoB oligonucleotide array hybridization patterns. Species identification for each of the isolates was similar irrespective of whether 16S sequence, rpoB sequence, or the pattern of rpoB hybridization was used. However for several species, the number of alleles in the 16S and rpoB gene sequences provided discordant estimates of the genetic diversity within a species. In addition to confirming the array's intended utility for sequencing the region of M. tuberculosis that confers rifampin resistance, this work demonstrates that this array can identify the species of nontuberculous ***Mycobacteria*** . This demonstrates the general point that DNA microarrays that sequence important genomic regions (such as drug resistance or pathogenicity islands) can simultaneously

identify species and provide some insight into the organism's population structure.

L2 ANSWER 23 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 17
AN 1998:207659 BIOSIS
DN PREV199800207659
TI Molecular beacon sequence analysis for detecting drug resistance in ***Mycobacterium*** tuberculosis.
AU Piatek, Amy S.; Tyagi, Sanjay; Pol, Arno C.; Telenti, Amalio; Miller, Lincoln P.; Kramer, Fred Russell; ***Alland, David (1)***
CS (1) Div. Infect. Dis., Dep. Med., Montefiore Med. Cent., Bronx, NY 10467 USA
SO Nature Biotechnology, (April, 1998) Vol. 16, No. 4, pp. 359-363.
ISSN: 1087-0156.
DT Article
LA English
AB We developed a new approach to DNA sequence analysis that uses fluorogenic reporter molecules-molecular beacons-and demonstrated their ability to discriminate alleles in real-time PCR assays of genomic DNA. A set of overlapping molecular beacons was used to analyze an 81-bp region of the ***Mycobacterium*** tuberculosis rpoB gone for mutations that confer resistance to the antibiotic rifampin. In a blinded study of 52 rifampin-resistant and 23 rifampin-susceptible clinical isolates, this method correctly detected mutations in all of the resistant strains and in none of the susceptible strains. The assay was carried out entirely in sealed PCR tubes and was simple to perform and interpret. This approach can be used to analyze any DNA sequence of moderate length with single base pair accuracy.

L2 ANSWER 24 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:415378 BIOSIS
DN PREV199800415378
TI Drug resistance and species identification in ***Mycobacterium*** infections greater than using oligonucleotide arrays.
AU Gingeras, Thomas R. (1); Ghandour, Ghassan (1); Wang, Eugene (1); Berno, Anthony (1); Small, Peter M.; Drobniewski, Francis; ***Alland, David*** ; Desmond, Edward; Holodniy, M.; Drenkow, J. (1)
CS (1) Affymetrix, Santa Clara, CA USA
SO Abstracts of the General Meeting of the American Society for Microbiology, (1998) Vol. 98, pp. 18.
Meeting Info.: 98th General Meeting of the American Society for Microbiology Atlanta, Georgia, USA May 17-21, 1998 American Society for Microbiology
. ISSN: 1060-2011.
DT Conference
LA English

L2 ANSWER 25 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 18
AN 1997:158521 BIOSIS
DN PREV199799457724
TI Exogenous reinfection with multidrug-resistant ***Mycobacterium*** tuberculosis.
AU Turett, Glenn S. (1); Fazal, B. A.; Justman, J. E.; ***Alland, D.*** ; Duncalf, R. M.; Telzak, E. E.
CS (1) Bronx-Lebanon Hosp. Cent., 8th Floor, Dep. Med., 1650 Grand Concourse

Bronx, NY 10457 USA
SO Clinical Infectious Diseases, (1997) Vol. 24, No. 3, pp. 513-514.
ISSN: 1058-4838.
DT (CASE STUDY)
LA English

L2 ANSWER 26 OF 37 LIFESCI COPYRIGHT 2003 CSA on STN DUPLICATE 19
AN 97:113238 LIFESCI
TI A city-wide outbreak of a multiple-drug-resistant strain of ***Mycobacterium*** tuberculosis in New York
AU Moss, A.R.; ***Alland, D.*** ; Telzak, E.; Hewlett, D.,Jr.; Sharp, V.; Chiliade, P.; LaBombardi, V.; Kabus, D.; Hanna, B.; Palumbo, L.; Brudney, K.; Weltman, A.; Stoeckle, K.; Chirgwin, K.; Simberkoff, M.; et al.
CS Dep. Epidemiol. and Biostatistics, UCSF, Box 1347, San Francisco, CA 94143-1347, USA
SO INT. J. TUBERC. LUNG DIS., (19970400) vol. 1, no. 2, pp. 115-121.
ISSN: 1027-3719.
DT Journal
FS J
LA English
SL English
AB SETTING: Incident patients with active tuberculosis (TB) resistant to two or more drugs in New York City hospitals in 1992. OBJECTIVE: To examine the New York-wide distribution of Public Health Research Institute (PHRI) strain W of ***Mycobacterium*** tuberculosis, an extremely drug-resistant strain identified by a 17-band Southern hybridization pattern using IS6110, during the peak tuberculosis year of 1992. We also compared strain W with other strains frequently observed in New York. DESIGN: Blinded retrospective study of stored M. tuberculosis cultures by restriction fragment length polymorphism (RFLP) DNA fingerprinting, and chart review. RESULTS: We found 112 cultures with the strain W fingerprint and 8 variants in 21 hospitals among incident patients hospitalized in 1992. Almost all isolates were resistant to four first-line drugs and kanamycin. This single strain made up at least 22% of New York City multiple-drug-resistant (MDR) TB in 1992, far more than any other strain. Almost all W-strain cases were acquired immune deficiency syndrome (AIDS) patients. The cluster is the most drug-resistant cluster identified in New York and the largest IS6110 fingerprint cluster identified anywhere to date. CONCLUSION: Because recommended four-drug therapy will not sterilise this very resistant strain, there was a city-wide nosocomial outbreak of W-strain TB in the early 1990s among New York AIDS patients. Other frequently seen strains were either also very resistant, or, surprisingly, pansusceptible. Individual MDR strains can be spread widely in situations where AIDS and TB are both common.

L2 ANSWER 27 OF 37 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN DUPLICATE 20
AN 97297810 EMBASE
DN 1997297810
TI Multiple drug resistance: A world-wide threat.
AU Warren R.M.; Shah S.S.; ***Alland D.***
CS Dr. R.M. Warren, MRC Ctr. for Molec./Cellular BIol., University of Stellenbosch, Faculty of Medicine, PO Box 19063, Tygerberg, Cape Town 7505, South Africa
SO Bailliere's Clinical Infectious Diseases, (1997) 4/1 (77-96).
Refs: 108
ISSN: 1071-6564 CODEN: BCIDFD

CY United Kingdom
DT Journal; General Review
FS 004 Microbiology
006 Internal Medicine
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB The emergence of drug-resistant ***Mycobacterium*** tuberculosis threatens the ability of existing health care programmes to treat tuberculosis effectively. ***Mycobacterium*** tuberculosis becomes drug resistant primarily through mutations within antituberculosis drug target genes; patient non-compliance with anti- tuberculosis therapy and/or inadequate drug levels promote the selection of these mutations. Drug-resistant tuberculosis can also occur via transmission of an already drug-resistant strain to a susceptible individual. Molecular epidemiology, together with drug sensitivity testing, has shown that transmission accounts for > 50% of the incidence of drug-resistant disease. This demonstrates the inability of current programmes to contain the spread of resistance. The success of future tuberculosis control will depend on a global commitment to directly observed therapy and further research into epidemiology, modern diagnostics and new treatments.

L2 ANSWER 28 OF 37 LIFESCI COPYRIGHT 2003 CSA on STN DUPLICATE 21
AN 97:58533 LIFESCI
TI A multi-institutional outbreak of highly drug-resistant tuberculosis. Epidemiology and clinical outcomes
AU Frieden, T.R.; Sherman, L.F.; Maw, K.L.; Fujiwara, P.I.; Crawford, J.T.; Nivin, B.; Sharp, V.; Hewlett, D.,Jr.; Brudney, K.; ***Alland, D.*** ; Kreiswirth, B.N.
CS Bureau Tuberculosis Control, New York City Dep. Health, 125 Worth St., Box 74, New York, NY 10013, USA
SO J. AM. MED. ASSOC., (1996) vol. 276, no. 15, pp. 1229-1235.
ISSN: 0098-7484.
DT Journal
FS J
LA English
SL English
AB We investigated a multi-institutional outbreak of highly resistant tuberculosis in every tuberculosis case reported in New York City for patients cared for at all public and nonpublic institutions from January 1, 1990, to August 1, 1993 (43 months). A case was defined as tuberculosis in a patient with an isolate resistant to isoniazid, rifampin, ethambutol hydrochloride, and streptomycin (and rifabutin, if sensitivity testing included it), and, if RFLP testing was done, a pattern identical to or closely related to strain W. Of the 357 patients who met the case definition, 267 had identical or nearly identical RFLP patterns; isolates from the other 90 patients were not available for RFLP testing. Among these 267 patients, 86% were human immunodeficiency virus (HIV)-infected, 7% were HIV-negative, and 7% had unknown HIV status. All-cause mortality was 83%. Epidemiologic linkages were identified for 70% of patients, of whom 96% likely had nosocomially acquired disease at 11 hospitals. Survival was prolonged among patients who recieved medications to which their isolate was susceptible, especially capreomycin sulfate, and among patients with a CD4 super(+) T-lymphocyte count greater than 0.200 x 10 super(9)/L (200/ mu L). Treatment with isoniazid and a fluoroquinolone antibiotic was also independently associated with longer survival. This

outbreak accounted for nearly one fourth of the cases of multidrug-resistant tuberculosis in the United States during a 43-month period. Most patients had nosocomially acquired disease, were infected with HIV, and unless promptly and appropriately treated, died rapidly. With appropriate directly observed treatment, especially combinations including an injectable medication, even severely immunocompromised patients had culture conversion and prolonged, tuberculosis-free survival.

L2 ANSWER 29 OF 37 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
DUPLICATE 22
AN 96053838 EMBASE
DN 1996053838
TI Clinical experience with rifampin-isoniazid-streptomycin-ethambutol (rise)-resistant tuberculosis.
AU Horn D.L.; Hewlett Jr. D.; Alfalla C.; Patel A.; Brudney K.; Crawford J.T.; ***Alland D.*** ; Kreiswirth B.; Opal S.M.; Peterson S.
CS Department of Medicine, Lincoln Medical/Mental Health Center, 234 East 149th Street,Bronx, NY 10451, United States
SO Infectious Diseases in Clinical Practice, (1996) 5/1 (68-72).
ISSN: 1056-9103 CODEN: IDCPEY
CY United States
DT Journal; Article
FS 004 Microbiology
015 Chest Diseases, Thoracic Surgery and Tuberculosis
017 Public Health, Social Medicine and Epidemiology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English
AB We review demographic and clinical features of 55 patients with rifampin-isoniazid-streptomycin-ethambutol (RISE)-resistant tuberculosis in our hospital from April 1, 1991, to July 31, 1993. Fifty-one of the 55 patients (median age, 36 years) were seropositive for human immunodeficiency virus (HIV), and 49 had AIDS. Among the HIV-infected patients, the median CD4 cell count was 31/mm3. Forty-two patients died during the study period. Exogenous reinfection or superinfection with RISE-resistant tuberculosis occurred in 12 of 55 patients with a prior history of tuberculosis infection or disease. Fourteen of 55 received appropriate therapy, eight of whom became culture negative after a median of 68 days. Twelve of the 14 appropriately treated patients survived at least 6 months. When appropriately managed, even severely immunosuppressed individuals with HIV infection may have their RISE-resistant tuberculosis successfully controlled or eradicated. This infection however, remains highly lethal in the majority of patients with AIDS. Patients remain infectious for prolonged periods, even after appropriate therapy has been initiated.

L2 ANSWER 30 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 23
AN 1996:28343 BIOSIS
DN PREV199698600478
TI Improved outcomes for patients with multidrug-resistant tuberculosis.
AU Turett, Glenn S. (1); Telzak, Edward E.; Torian, Lucia V.; Blum, Steve; ***Alland, David*** ; Weisfuse, Isaac; Fazal, Barkat A.
CS (1) Bronx-Lebanan Hosp. Center, 8th Floor Dep. Med., 1650 Grand Concourse, Bronx, NY 10457 USA
SO Clinical Infectious Diseases, (1995) Vol. 21, No. 5, pp. 1238-1244.

ISSN: 1058-4838.
DT Article
LA English
AB We conducted a retrospective study of patients with culture-confirmed multidrug-resistant tuberculosis (MDR-TB) at Bronx-Lebanon Hospital Center (South Bronx, NY) to determine what factors affected clinical and microbiological responses and survival. For the 38 patients with MDR-TB, reporting of first-line drug susceptibilities was relatively rapid (median time, 30 days). Thirty-four patients (89%) were infected with human immunodeficiency virus (HIV), and initial and overall response rates were 59% and 50%, respectively; the median survival was 315 days; and 50% of these patients died of tuberculosis. Bivariate analysis revealed that the following factors had a positive impact on response and survival: receiving gtoreq 2 consecutive weeks of appropriate therapy with at least two drugs to which the isolate was susceptible in vitro; starting appropriate therapy within 4 weeks of the diagnosis; and having tuberculosis that was limited to the lungs. Multivariate analysis revealed that the only variable associated with response was receipt of appropriate therapy for gtoreq 2 consecutive weeks. In contrast to findings in the published literature, our results indicate the outcome of MDR-TB can be improved, particularly for severely immunosuppressed HIV-infected patients. Rapid reporting of susceptibilities and prompt initiation and continuation of appropriate antituberculous therapy improved response and survival.

L2 ANSWER 31 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 24
AN 1994:321497 BIOSIS
DN PREV199497334497
TI Transmission of tuberculosis in New York City: An analysis by DNA fingerprinting and conventional epidemiologic methods.
AU ***Alland, David (1)*** ; Kalkut, Gary E.; Moss, Andrew R.; McAdam, Ruth A.; Hahn, Judith A.; Bosworth, William; Drucker, Ernest; Bloom, Barry R.
CS (1) Div. Infectious Diseases, Dep. Med., Montefiore Med. Cent., 111 East 210 St., Bronx, NY 10467 USA
SO New England Journal of Medicine, (1994) Vol. 330, No. 24, pp. 1710-1716. ISSN: 0028-4793.
DT Article
LA English
AB Background: The incidence of tuberculosis and drug resistance is increasing in the United States, but it is not clear how much of the increase is due to reactivation of latent infection and how much to recent transmission. Methods: We performed DNA fingerprinting using restriction-fragment-length polymorphism (RFLP) analysis of at least one isolate from every patient with confirmed tuberculosis at a major hospital in the Bronx, New York, (USA) from December 1, 1989, through December 31, 1992. Medical records and census-tract data were reviewed for relevant clinical, social, and demographic data. Results: Of 130 patients with tuberculosis, 104 adults (80 percent) had complete medical records and isolates whose DNA fingerprints could be evaluated. Isolates from 65 patients (62.5 percent) had unique RFLP patterns, whereas isolates from 39 patients (37.5 percent) had RFLP patterns that were identical to those of an isolate from at least 1 other study patient; the isolates in the latter group were classified into 12 clusters. Patients whose isolates were included in one of the clusters were inferred to have recently transmitted disease. Independent risk factors for having a clustered isolate included

seropositivity for the human immunodeficiency virus (HIV) (odds ratio for Hispanic patients, 4.31; P = 0.02; for non-Hispanic patients, 3.12; P = 0.07), Hispanic ethnicity combined with HIV seronegativity (odds ratio, 5.13; P = 0.05), infection with drug-resistant tuberculosis (odds ratio, 4.52; P = 0.005), and younger age (odds ratio, 1.59; P = 0.02). Residence in sections of the Bronx with a median household income below 20,000 was also associated with having a clustered isolate (odds ratio, 3.22; P = 0.04). Conclusions: In the inner-city community we studied, recently transmitted tuberculosis accounts for approximately 40 percent of the incident cases and almost two thirds of drug-resistant cases. Recent transmission of tuberculosis, and not only reactivation of latent disease, contributes substantially to the increase in tuberculosis.

L2 ANSWER 32 OF 37 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
AN 94319472 EMBASE
DN 1994319472
TI Transmission of tuberculosis [1].
AU McKenna M.; Williams Jr. M.H.; Pollen R.H.; Joy M.; Small P.M.; Hopewell P.C.; Schoolnik G.K.; Kalkut G.E.; ***Alland D.*** ; Bloom B.R.; Frieden T.R.; Hamburg M.A.
CS Ctrs. for Disease Control/Prevention,Atlanta, GA 30333, United States
SO New England Journal of Medicine, (1994) 331/16 (1093-1096).
ISSN: 0028-4793 CODEN: NEJMAG
CY United States
DT Journal; Letter
FS 004 Microbiology
017 Public Health, Social Medicine and Epidemiology
037 Drug Literature Index
LA English

L2 ANSWER 33 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1994:427690 BIOSIS
DN PREV199497440690
TI Recently transmitted tuberculosis in the Bronx: Multi-drug resistance as part of a larger picture.
AU ***Alland, D. (1)*** ; Kalcut, G. (1); Moss, A.; McAdam, R.; Drucker, E. (1); Bosworth, W.; Hahn, J.; Motyl, M.; Bloom, B.
CS (1) Montefiore Med. Cent., New York, NY USA
SO Program and Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, (1993) Vol. 33, No. 0, pp. 443.
Meeting Info.: 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy New Orleans, Louisiana, USA October 17-20, 1993
ISSN: 0733-6373.
DT Conference
LA English

L2 ANSWER 34 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1993:445910 BIOSIS
DN PREV199345081535
TI Detection by DNA fingerprinting (DNA FP) of a "hidden" tuberculosis outbreak among HIV-positive homeless patients.
AU Dobkin, J. (1); Bangsberg, D.; Brudney, K. (1); Kalkut, G.; Bloom, B.; ***Alland, D.***
CS (1) Columbia Coll. Physicians and Surgeons, Albert Einstein Coll. Med., NY, NY USA
SO IXTH INTERNATIONAL CONFERENCE ON AIDS AND THE IVTH STD WORLD CONGRESS.. (1993) pp. 324. IXth International Conference on AIDS in affiliation with

the IVth STD World Congress.
Publisher: IXth International Conference on AIDS Berlin, Germany.
Meeting Info.: Meeting Berlin, Germany June 6-11, 1993
DT Conference
LA English

L2 ANSWER 35 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1992:119143 BIOSIS
DN BA93:64943
TI A MAJOR T CELL ANTIGEN OF ***MYCOBACTERIUM*** -LEPRAE IS A 10-KD HEAT-SHOCK COGNATE PROTEIN.
AU MEHRA V; BLOOM B R; BAJARDI A C; GRISSO C L; SIELING P A; ***ALLAND D*** ; CONVIT J; FAN X; HUNTER S W; ET AL
CS INQ.: PATRICK J. BRENNAN, DEP. MICROBIOL., COLORADO STATE UNIVERSITY, FORT COLLINS, COLO. 80523.
SO J EXP MED, (1992) 175 (1), 276-284.
CODEN: JEMEAV. ISSN: 0022-1007.
FS BA; OLD
LA English
AB Several ***mycobacterial*** antigens, identified by monoclonal antibodies and patient sera, have been found to be homologous to stress or heat-shock proteins (hsp) defined in Escherichia coli and yeast. A major antigen recognized by most ***Mycobacterium*** leprae-reactive human T cell lines and cell wall-reactive T cell clones is a 10-kD protein that has now been cloned and sequenced. The predicted amino acid sequence of this protein is 44% homologous to the hsp 10 (GroES) of E. coli. The purified native and recombinant 10-kD protein was found to be a stronger stimulator of peripheral blood T cell proliferation than other native and recombinant M. leprae proteins tested. The degree of reactivity paralleled the response to intact M. leprae throughout the spectrum of leprosy. Limiting-dilution analysis of peripheral blood lymphocytes from a patient contact and a tuberculoid patient indicated that approximately one third of M. leprae-reactive T cell precursors responded to the 10-kD antigen. T cell lines derived from lepromin skin tests were strongly responsive to the 10-kD protein. T cell clones reactive to both the purified native and recombinant 10-kD antigens recognized M. leprae-specific epitopes as well as epitopes crossreactive with the cognate antigen of M. tuberculosis. Further, the purified hsp 10 elicited strong delayed-type hypersensitivity reactions in guinea pigs sensitized to M. leprae. The strong T cell responses against the M. leprae 10-kD protein suggest a role for this heat-shock cognate protein in the protective/resistant responses to infection.

L2 ANSWER 36 OF 37 CAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 25
AN 1992:446378 CAPLUS
DN 117:46378
TI A major T cell antigen of ***Mycobacterium*** leprae is a 10-kD heat-shock cognate protein
AU Mehra, Vijay; Bloom, Barry R.; Bajardi, Adriana C.; Grisso, Cara L.; Sieling, Peter A.; ***Alland, David*** ; Convit, Jacinto; Fan, Xuedong; Hunter, Shirley W.; et al.
CS Dep. Microbiol. Immunol., Albert Einstein Coll. Med., Bronx, NY, 10461, USA
SO Journal of Experimental Medicine (1992), 175(1), 275-84
CODEN: JEMEAV; ISSN: 0022-1007
DT Journal
LA English

AB Several ***mycobacterial*** antigens, identified by monoclonal antibodies and patient sera, have been found to be homologous to stress or heat-shock proteins (hsp) defined in Escherichia coli and yeast. A major antigen recognized by most M. leprae-reactive human T cell lines and cell wall-reactive T cell clones is a 10-kD protein that has now been cloned and sequenced. The predicted amino acid sequence of this protein is 44% homologous to the hsp 10 (GroES) of E. coli. The purified native and recombinant 10-kD protein was a stronger stimulator of peripheral blood T cell proliferation than other native and recombinant M. leprae proteins tested. The degree of reactivity paralleled the response to intact M. leprae throughout the spectrum of leprosy. Limiting-diln. anal. of peripheral blood lymphocytes from a patient contact and a tuberculoid patient indicated that approx. one third of M. leprae-reactive T cell precursors responded to the 10-kD antigen. T cell lines derived from lepromin skin tests were strongly responsive to the 10-kD protein. T cell clones reactive to both the purified native and recombinant 10-kD antigens recognized M. leprae-specific epitopes as well as epitopes cross-reactive with the cognate antigen of M. tuberculosis. Further, the purified hsp 10 elicited strong delayed-type hypersensitivity reactions in guinea pigs sensitized to M. leprae. The strong T cell responses against the M. leprae 10-kD protein suggest a role for this heat-shock cognate protein in the protective/resistant responses to infection.

L2 ANSWER 37 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1991:446213 BIOSIS
DN BR41:83948
TI PROSPECTIVE STUDY OF TUBERCULOSIS RISK IN A COHORT OF HIV SEROPOSITIVE WOMEN IN KIGALI RWANDA.
AU KAGAME A; BATUNGWAMAYO J; ALLEN S; BOGAERTS J; TAELMAN H; ***ALLAND D*** ; BLANCHE P; SERUFFILIRA A; NSENGUMUREMYI F; BLACK D; HULLEY S; VAN DE PERRE P
CS CENTRE HOSPITALIER DE KIGALI, KIGALI, RWANDA.
SO ISTITUTO SUPERIORE DI SANITA. VII INTERNATIONAL CONFERENCE ON AIDS: SCIENCE CHALLENGING AIDS; FLORENCE, ITALY, JUNE 16-21, 1991. 464P.(VOL. 1); 460P.(VOL. 2). ISTITUTO SUPERIORE DI SANITA: ROME, ITALY. PAPER. (1991) 0 (0), 80B.
DT Conference
FS BR; OLD
LA English

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=> e bloom barry/au
E1          338     BLOOM B S/AU
E2           63     BLOOM B T/AU
E3           15 --> BLOOM BARRY/AU
E4            4     BLOOM BARRY IRVING/AU
E5           53     BLOOM BARRY M/AU
E6          338     BLOOM BARRY R/AU
E7           20     BLOOM BARRY T/AU
E8            1     BLOOM BARRY THEIL/AU
E9           32     BLOOM BEN/AU
E10           1     BLOOM BEN P/AU
E11           1     BLOOM BENJAMIN H/AU
E12           4     BLOOM BENSON/AU

=> s e1-e8 and mycobact?
L3          203 ("BLOOM B S"/AU OR "BLOOM B T"/AU OR "BLOOM BARRY"/AU OR "BLOOM
```

BARRY IRVING"/AU OR "BLOOM BARRY M"/AU OR "BLOOM BARRY R"/AU OR "BLOOM BARRY T"/AU OR "BLOOM BARRY THEIL"/AU) AND MYCOBACT?

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4 148 DUP REM L3 (55 DUPLICATES REMOVED)

=> s l4 and (iniB or iniA or iniC)
L5 4 L4 AND (INIB OR INIA OR INIC)

=> d bib ab 1-
YOU HAVE REQUESTED DATA FROM 4 ANSWERS - CONTINUE? Y/(N):y

L5 ANSWER 1 OF 4 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:455186 BIOSIS
DN PREV200100455186
TI ***IniB*** , ***iniA*** and ***iniC*** genes of ***mycobacteria*** and methods of use.
AU Alland, David; ***Bloom, Barry R.*** ; Jacobs, William R., Jr.
CS Dobbs Ferry, NY USA
ASSIGNEE: Albert Einstein College of Medicine of Yeshiva University
PI US 6268201 July 31, 2001.
SO Official Gazette of the United States Patent and Trademark Office Patents, (July 31, 2001) Vol. 1248, No. 5, pp. No Pagination. e-file.
ISSN: 0098-1133.
DT Patent
LA English
AB This invention relates to the identification, cloning, sequencing and characterization of the ***iniB*** , ***iniA*** and ***iniC*** genes of ***mycobacteria*** which are induced by a broad class of antibiotics that act by inhibiting cell wall biosynthesis, including the first line antituberculosis agents, isoniazid and ethambutol. The present invention provides purified and isolated ***iniB*** , ***iniA*** , ***iniC*** and ***iniB*** promoter nucleic acids which may comprise the iniBAC operon, as well as mutated forms of these nucleic acids. The present invention also provides one or more single-stranded nucleic acid probes which specifically hybridize to the ***iniB*** , ***iniA*** , ***iniC*** and ***iniB*** promoter nucleic acids, and mixtures thereof, which may be formulated in kits, and used in the diagnosis of drug-resistant ***mycobacterial*** strain. The present invention also provides methods for the screening and identification of drugs effective against ***Mycobacterium*** tuberculosis using induction of the ***iniB*** promoter.

L5 ANSWER 2 OF 4 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:378898 BIOSIS
DN PREV200000378898
TI Identification and characterization of a ***Mycobacterium*** tuberculosis promoter that is induced by a broad range of antibiotics that inhibit cell wall biosynthesis.
AU Alland, David (1); Cerny, Rosaria (1); Steyn, Adrie J.; Weisbrod, Torin; ***Bloom, Barry R.*** ; Jacobs, William R., Jr.
CS (1) Division of Infectious Diseases, Montefiore Medical Center, Bronx, NY, 10467 USA
SO Tubercle and Lung Disease, (2000) Vol. 80, No. 2, pp. 85-86. print.
Meeting Info.: Tuberculosis-Leprosy Panel's 34th Annual Research Conference on the US-Japan Cooperative Medical Science Program San

Francisco, California, USA June 27-30, 1999
ISSN: 0962-8479.
DT Conference
LA English
SL English

L5 ANSWER 3 OF 4 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1999:4927 BIOSIS
DN PREV199900004927
TI Identification of differentially expressed mRNA in prokaryotic organisms by customized amplification libraries (DECAL): The effect of isoniazid on gene expression in ***Mycobacterium*** tuberculosis.
AU Alland, David (1); Kramnik, Igor; Weisbrod, Torin R.; Otsubo, Lisa; Cerny, Rosaria; Miller, Lincoln P.; Jacobs, William R., Jr.; ***Bloom, Barry*** *** R.***
CS (1) Div. Infectious Disease, Montefiore Medical Cent., 111 East 210th St., Bronx, NY 10467 USA
SO Proceedings of the National Academy of Sciences of the United States of America, (Oct. 27, 1998) Vol. 95, No. 22, pp. 13227-13232.
ISSN: 0027-8424.
DT Article
LA English
AB Understanding the effects of the external environment on bacterial gene expression can provide valuable insights into an array of cellular mechanisms including pathogenesis, drug resistance, and, in the case of ***Mycobacterium*** tuberculosis, latency. Because of the absence of poly(A)+ mRNA in prokaryotic organisms, studies of differential gene expression currently must be performed either with large amounts of total RNA or rely on amplification techniques that can alter the proportional representation of individual mRNA sequences. We have developed an approach to study differences in bacterial mRNA expression that enables amplification by the PCR of a complex mixture of cDNA sequences in a reproducible manner that obviates the confounding effects of selected highly expressed sequences, e.g., ribosomal RNA. Differential expression using customized amplification libraries (DECAL) uses a library of amplifiable genomic sequences to convert total cellular RNA into an amplified probe for gene expression screens. DECAL can detect 4-fold differences in the mRNA levels of rare sequences and can be performed on as little as 10 ng of total RNA. DECAL was used to investigate the in vitro effect of the antibiotic isoniazid on M. tuberculosis, and three previously uncharacterized isoniazid-induced genes, ***iniA*** , ***iniB*** , and ***iniC*** , were identified. The ***iniB*** gene has homology to cell wall proteins, and ***iniA*** contains a phosphopantetheine attachment site motif suggestive of an acyl carrier protein. The ***iniA*** gene is also induced by the antibiotic ethambutol, an agent that inhibits cell wall biosynthesis by a mechanism that is distinct from isoniazid. The DECAL method offers a powerful new tool for the study of differential gene expression.

L5 ANSWER 4 OF 4 USPATFULL on STN
AN 2002:272887 USPATFULL
TI ***IniB*** , ***iniA*** and ***iniC*** genes of ***mycobacteria*** and methods of use
IN Alland, David, Dobbs Ferry, NY, UNITED STATES
Bloom, Barry R. , Hastings-on-Hudson, NY, UNITED STATES
Jacobs, William R., JR., City Island, NY, UNITED STATES

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PI     US 2002151008      A1   20021017
AI     US 2001-918951     A1   20010731 (9)
RLI    Continuation of Ser. No. US 1998-177349, filed on 23 Oct 1998, PATENTED
DT     Utility
FS     APPLICATION
LREP   Elie H. Gendloff, Ph.D., Esq., AMSTER, ROTHSTEIN & EBENSTEIN, 90 Park
       Avenue, New York, NY, 10016
CLMN   Number of Claims: 47
ECL    Exemplary Claim: 1
DRWN   10 Drawing Page(s)
LN.CNT 935
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB     This invention relates to the identification, cloning, sequencing and
       characterization of the   ***iniB***  ,   ***iniA***   and   ***iniC***
       genes of   ***mycobacteria***   which are induced by a broad class of
       antibiotics that act by inhibiting cell wall biosynthesis, including the
       first line antituberculosis agents, isoniazid and ethambutol. The
       present invention provides purified and isolated   ***iniB***  ,
         ***iniA***  ,   ***iniC***   and   ***iniB***   promoter nucleic acids
       which may comprise the iniBAC operon, as well as mutated forms of these
       nucleic acids. The present invention also provides one or more
       single-stranded nucleic acid probes which specifically hybridize to the
         ***iniB***  ,   ***iniA***  ,   ***iniC***   and   ***iniB***
promoter
       nucleic acids, and mixtures thereof, which may be formulated in kits,
       and used in the diagnosis of drug-resistant   ***mycobacterial***
       strain. The present invention also provides methods for the screening
       and identification of drugs effective against   ***Mycobacterium***
       tuberculosis using induction of the   ***iniB***   promoter.


=> e jacobs william/au
E1            1     JACOBS WILLI/AU
E2            2     JACOBS WILLI F/AU
E3           25 --> JACOBS WILLIAM/AU
E4            8     JACOBS WILLIAM A/AU
E5            1     JACOBS WILLIAM ALAN/AU
E6           20     JACOBS WILLIAM B/AU
E7            1     JACOBS WILLIAM BARRY/AU
E8           13     JACOBS WILLIAM D/AU
E9            7     JACOBS WILLIAM E/AU
E10           1     JACOBS WILLIAM EDWARD/AU
E11           4     JACOBS WILLIAM F/AU
E12           3     JACOBS WILLIAM F III/AU

=> s e1-e12 and mycobact?
L6            1 ("JACOBS WILLI"/AU OR "JACOBS WILLI F"/AU OR "JACOBS WILLIAM"/AU
                 OR "JACOBS WILLIAM A"/AU OR "JACOBS WILLIAM ALAN"/AU OR "JACOBS
                 WILLIAM B"/AU OR "JACOBS WILLIAM BARRY"/AU OR "JACOBS WILLIAM
               D"/AU OR "JACOBS WILLIAM E"/AU OR "JACOBS WILLIAM EDWARD"/AU OR
               "JACOBS WILLIAM F"/AU OR "JACOBS WILLIAM F III"/AU) AND MYCOBACT
               ?

=> e jabcobs william r/au
E1            1     JABCOB J C/AU
E2            1     JABCOB JUERGEN/AU
E3            0 --> JABCOBS WILLIAM R/AU
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E4            6      JABCOBSON M R/AU
E5            1      JABCOBSON S J/AU
E6            1      JABCON JR LEONARD J/AU
E7            2      JABCON LEONARD J/AU
E8            3      JABCONOVA A/AU
E9            4      JABCONOVA ADRIANA/AU
E10           1      JABCZENSKI A/AU
E11           1      JABCZENSKI F/AU
E12           3      JABCZENSKI F F/AU

=> e jacobs william R/au
E1           44      JACOBS WILLIAM P/AU
E2            2      JACOBS WILLIAM PAUL/AU
E3           74 --> JACOBS WILLIAM R/AU
E4          268      JACOBS WILLIAM R JR/AU
E5            1      JACOBS WILLIAM REESE/AU
E6            1      JACOBS WILLIAM REID JR/AU
E7            3      JACOBS WILLIAM ROBERT/AU
E8            4      JACOBS WILLIAM S/AU
E9            4      JACOBS WILLIAM W/AU
E10           1      JACOBS WILLIAM WESCOTT/AU
E11           1      JACOBS WILLIAMS R/AU
E12           1      JACOBS WILLIE/AU

=> s e3-e7 and mycobact?
L7          301 ("JACOBS WILLIAM R"/AU OR "JACOBS WILLIAM R JR"/AU OR "JACOBS
                WILLIAM REESE"/AU OR "JACOBS WILLIAM REID JR"/AU OR "JACOBS
                WILLIAM ROBERT"/AU) AND MYCOBACT?

=> s l7 and (iniB or iniA or iniC)
L8            8 L7 AND (INIB OR INIA OR INIC)

=> dup rem l8
PROCESSING COMPLETED FOR L8
L9            5 DUP REM L8 (3 DUPLICATES REMOVED)

=> d bib ab 1-
YOU HAVE REQUESTED DATA FROM 5 ANSWERS - CONTINUE? Y/(N):y

L9   ANSWER 1 OF 5  USPATFULL on STN
AN     2002:272887  USPATFULL
TI       ***IniB***  ,   ***iniA***   and   ***iniC***   genes of
         ***mycobacteria***   and methods of use
IN     Alland, David, Dobbs Ferry, NY, UNITED STATES
       Bloom, Barry R., Hastings-on-Hudson, NY, UNITED STATES
           ***Jacobs, William R., JR.***  , City Island, NY, UNITED STATES
PI     US 2002151008      A1   20021017
AI     US 2001-918951     A1   20010731 (9)
RLI    Continuation of Ser. No. US 1998-177349, filed on 23 Oct 1998, PATENTED
DT     Utility
FS     APPLICATION
LREP   Elie H. Gendloff, Ph.D., Esq., AMSTER, ROTHSTEIN & EBENSTEIN, 90 Park
       Avenue, New York, NY, 10016
CLMN   Number of Claims: 47
ECL    Exemplary Claim: 1
DRWN   10 Drawing Page(s)
LN.CNT 935
```

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to the identification, cloning, sequencing and characterization of the ***iniB*** , ***iniA*** and ***iniC*** genes of ***mycobacteria*** which are induced by a broad class of antibiotics that act by inhibiting cell wall biosynthesis, including the first line antituberculosis agents, isoniazid and ethambutol. The present invention provides purified and isolated ***iniB*** , ***iniA*** , ***iniC*** and ***iniB*** promoter nucleic acids which may comprise the iniBAC operon, as well as mutated forms of these nucleic acids. The present invention also provides one or more single-stranded nucleic acid probes which specifically hybridize to the ***iniB*** , ***iniA*** , ***iniC*** and ***iniB*** promoter nucleic acids, and mixtures thereof, which may be formulated in kits, and used in the diagnosis of drug-resistant ***mycobacterial*** strain. The present invention also provides methods for the screening and identification of drugs effective against ***Mycobacterium*** tuberculosis using induction of the ***iniB*** promoter.

L9 ANSWER 2 OF 5 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 1

AN 2001:455186 BIOSIS

DN PREV200100455186

TI ***IniB*** , ***iniA*** and ***iniC*** genes of ***mycobacteria*** and methods of use.

AU Alland, David; Bloom, Barry R.; ***Jacobs, William R., Jr.***

CS Dobbs Ferry, NY USA
ASSIGNEE: Albert Einstein College of Medicine of Yeshiva University

PI US 6268201 July 31, 2001

SO Official Gazette of the United States Patent and Trademark Office Patents, (July 31, 2001) Vol. 1248, No. 5, pp. No Pagination. e-file.
ISSN: 0098-1133.

DT Patent

LA English

AB This invention relates to the identification, cloning, sequencing and characterization of the ***iniB*** , ***iniA*** and ***iniC*** genes of ***mycobacteria*** which are induced by a broad class of antibiotics that act by inhibiting cell wall biosynthesis, including the first line antituberculosis agents, isoniazid and ethambutol. The present invention provides purified and isolated ***iniB*** , ***iniA*** , ***iniC*** and ***iniB*** promoter nucleic acids which may comprise the iniBAC operon, as well as mutated forms of these nucleic acids. The present invention also provides one or more single-stranded nucleic acid probes which specifically hybridize to the ***iniB*** , ***iniA*** , ***iniC*** and ***iniB*** promoter nucleic acids, and mixtures thereof, which may be formulated in kits, and used in the diagnosis of drug-resistant ***mycobacterial*** strain. The present invention also provides methods for the screening and identification of drugs effective against ***Mycobacterium*** tuberculosis using induction of the ***iniB*** promoter.

L9 ANSWER 3 OF 5 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 2

AN 2000:179354 BIOSIS

DN PREV200000179354

TI Characterization of the ***Mycobacterium*** tuberculosis iniBAC promoter, a promoter that responds to cell wall biosynthesis inhibition.

AU Alland, David (1); Steyn, Andries J.; Weisbrod, Torin; Aldrich, Kate; ***Jacobs, William R., Jr.***

CS (1) Division of Infectious Diseases, Montefiore Medical Center, 111 East 210th St., Centennial Building 4th floor, Bronx, NY, 10467 USA

SO Journal of Bacteriology, (April, 2000) Vol. 182, No. 7, pp. 1802-1811. ISSN: 0021-9193.

DT Article

LA English

SL English

AB The cell wall provides an attractive target for antibiotics against ***Mycobacterium*** tuberculosis. Agents such as isoniazid and ethambutol that work by inhibiting cell wall biosynthesis are among the most highly effective antibiotics against this pathogen. Although considerable progress has been made identifying the targets for cell wall active antibiotics, little is known about the intracellular mechanisms that are activated as a consequence of cell wall injury. These mechanisms are likely to have an important role in growth regulation and in the induction of cell death by antibiotics. We previously discovered three isoniazid-induced genes (***iniB*** , ***iniA*** , and ***iniC***) organized in tandem on the M. tuberculosis genome. Here, we investigate the unique features of the putative iniBAC promoter. This promoter was specifically induced by a broad range of inhibitors of cell wall biosynthesis but was not inducible by other conditions that are toxic to ***mycobacteria*** via other mechanisms. Induction required inhibitory concentrations of antibiotics and could be detected only in actively growing cells. Analysis of the iniBAC promoter sequence revealed both a regulatory element upstream and a potential repressor binding region downstream of the transcriptional start site. The induction phenotype and structure of the iniBAC promoter suggest that a complex intracellular response occurs when cell wall biosynthesis is inhibited in M. tuberculosis and other ***mycobacteria*** .

L9 ANSWER 4 OF 5 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

AN 2000:378898 BIOSIS

DN PREV200000378898

TI Identification and characterization of a ***Mycobacterium*** tuberculosis promoter that is induced by a broad range of antibiotics that inhibit cell wall biosynthesis.

AU Alland, David (1); Cerny, Rosaria (1); Steyn, Adrie J.; Weisbrod, Torin; Bloom, Barry R.; ***Jacobs, William R., Jr.***

CS (1) Division of Infectious Diseases, Montefiore Medical Center, Bronx, NY, 10467 USA

SO Tubercle and Lung Disease, (2000) Vol. 80, No. 2, pp. 85-86. print. Meeting Info.: Tuberculosis-Leprosy Panel's 34th Annual Research Conference on the US-Japan Cooperative Medical Science Program San Francisco, California, USA June 27-30, 1999 ISSN: 0962-8479.

DT Conference

LA English

SL English

L9 ANSWER 5 OF 5 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 3

AN 1999:4927 BIOSIS

DN PREV199900004927

TI Identification of differentially expressed mRNA in prokaryotic organisms by customized amplification libraries (DECAL): The effect of isoniazid on

gene expression in ***Mycobacterium*** tuberculosis.
AU Alland, David (1); Kramnik, Igor; Weisbrod, Torin R.; Otsubo, Lisa; Cerny, Rosaria; Miller, Lincoln P.; ***Jacobs, William R., Jr.*** ; Bloom, Barry R.
CS (1) Div. Infectious Disease, Montefiore Medical Cent., 111 East 210th St., Bronx, NY 10467 USA
SO Proceedings of the National Academy of Sciences of the United States of America, (Oct. 27, 1998) Vol. 95, No. 22, pp. 13227-13232. ISSN: 0027-8424.
DT Article
LA English
AB Understanding the effects of the external environment on bacterial gene expression can provide valuable insights into an array of cellular mechanisms including pathogenesis, drug resistance, and, in the case of ***Mycobacterium*** tuberculosis, latency. Because of the absence of poly(A)+ mRNA in prokaryotic organisms, studies of differential gene expression currently must be performed either with large amounts of total RNA or rely on amplification techniques that can alter the proportional representation of individual mRNA sequences. We have developed an approach to study differences in bacterial mRNA expression that enables amplification by the PCR of a complex mixture of cDNA sequences in a reproducible manner that obviates the confounding effects of selected highly expressed sequences, e.g., ribosomal RNA. Differential expression using customized amplification libraries (DECAL) uses a library of amplifiable genomic sequences to convert total cellular RNA into an amplified probe for gene expression screens. DECAL can detect 4-fold differences in the mRNA levels of rare sequences and can be performed on as little as 10 ng of total RNA. DECAL was used to investigate the in vitro effect of the antibiotic isoniazid on M. tuberculosis, and three previously uncharacterized isoniazid-induced genes, ***iniA*** , ***iniB*** , and ***iniC*** , were identified. The ***iniB*** gene has homology to cell wall proteins, and ***iniA*** contains a phosphopantetheine attachment site motif suggestive of an acyl carrier protein. The ***iniA*** gene is also induced by the antibiotic ethambutol, an agent that inhibits cell wall biosynthesis by a mechanism that is distinct from isoniazid. The DECAL method offers a powerful new tool for the study of differential gene expression.

=> s mycobact? and (iniB or iniA or iniC)
L10 39 MYCOBACT? AND (INIB OR INIA OR INIC)

=> dup rem l10
PROCESSING COMPLETED FOR L10
L11 17 DUP REM L10 (22 DUPLICATES REMOVED)

=> d bib ab kwic 1-
YOU HAVE REQUESTED DATA FROM 17 ANSWERS - CONTINUE? Y/(N):y

L11 ANSWER 1 OF 17 USPATFULL on STN
AN 2003:120200 USPATFULL
TI Nucleic acids, proteins, and antibodies
IN Rosen, Craig A., Laytonsville, MD, UNITED STATES
Ruben, Steven M., Olney, MD, UNITED STATES
Barash, Steven C., Rockville, MD, UNITED STATES
PA Human Genome Sciences, Inc., Rockville, MD, 20850 (U.S. corporation)

PI	US 2003082681	A1	20030501
AI	US 2002-91391	A1	20020307 (10)
RLI	Continuation of Ser. No. US 2001-764903, filed on 17 Jan 2001, PENDING		
PRAI	US 2000-179065P	20000131 (60)	
	US 2000-180628P	20000204 (60)	
	US 2000-214886P	20000628 (60)	
	US 2000-217487P	20000711 (60)	
	US 2000-225758P	20000814 (60)	
	US 2000-220963P	20000726 (60)	
	US 2000-217496P	20000711 (60)	
	US 2000-225447P	20000814 (60)	
	US 2000-218290P	20000714 (60)	
	US 2000-225757P	20000814 (60)	
	US 2000-226868P	20000822 (60)	
	US 2000-216647P	20000707 (60)	
	US 2000-225267P	20000814 (60)	
	US 2000-216880P	20000707 (60)	
	US 2000-225270P	20000814 (60)	
	US 2000-251869P	20001208 (60)	
	US 2000-235834P	20000927 (60)	
	US 2000-234274P	20000921 (60)	
	US 2000-234223P	20000921 (60)	
	US 2000-228924P	20000830 (60)	
	US 2000-224518P	20000814 (60)	
	US 2000-236369P	20000929 (60)	
	US 2000-224519P	20000814 (60)	
	US 2000-220964P	20000726 (60)	
	US 2000-241809P	20001020 (60)	
	US 2000-249299P	20001117 (60)	
	US 2000-236327P	20000929 (60)	
	US 2000-241785P	20001020 (60)	
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US 2000-235484P 20000926 (60)
US 2000-190076P 20000317 (60)
US 2000-209467P 20000607 (60)
US 2000-205515P 20000519 (60)
US 2001-259678P 20010105 (60)
DT Utility
FS APPLICATION
LREP HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
CLMN Number of Claims: 24
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 21414
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to novel proteins. More specifically, isolated nucleic acid molecules are provided encoding novel polypeptides. Novel polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human polynucleotides and/or polypeptides, and antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to these novel polypeptides. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.
SUMM . . . Bluescript SK-
L0418 b4HB3MA-Cot109 + 10-
Lafmid BA
Bio
L0438 normalized infant brain total brain brain
lafmid BA
cDNA
L0439 Soares infant brain ***INIB***
whole brain Lafmid BA
L0456 Human retina cDNA retina eye
lambda gt10

Tsp5091-cleaved
sublibrary
L0471 Human fetal heart,
Lambda ZAP
Lambda ZAP. . .
SUMM . . . enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: Vibrio cholerae, ***Mycobacterium*** leprae, Salmonella typhi, Salmonella paratyphi, Meisseria meningitidis, Streptococcus pneumoniae, Group B streptococcus, Shigella spp., Enterotoxigenic Escherichia coli, Enterohemorrhagic E. coli,. . .
SUMM . . . . Yersinia, Shigella), Erysipelothrix, Haemophilus (e.g., Haemophilus influenza type B), Helicobacter, Legionella (e.g., Legionella pneumophila), Leptospira, Listeria (e.g., Listeria monocytogenes), Mycoplasma, ***Mycobacterium*** (e.g., ***Mycobacterium*** leprae and ***Mycobacterium*** tuberculosis), Vibrio (e.g., Vibrio cholerae), Neisseriaceae (e.g., Neisseria gonorrhea, Neisseria meningitidis), Pasteurellacea, Proteus, Pseudomonas (e.g., Pseudomonas aeruginosa), Rickettsiaceae, Spirochetes (e.g.,. . .
DETD . . . the invention are used in any combination with ISONIAZID.TM., RIFANIPIN.TM., PYRAZINAMIDE.TM., and/or ETHAMBUTOL.TM. to prophylactically treat or prevent an opportunistic ***Mycobacterium*** avium complex infection. In another specific embodiment, Therapeutics of the invention are used in any combination with RIFABUTIN.TM., CLARITHROMYCIN.TM., and/or AZITHROMYCIN.TM. to prophylactically treat or prevent an opportunistic ***Mycobacterium*** tuberculosis infection. In another specific embodiment, Therapeutics of the invention are used in any combination with GANCICLOVIR.TM., FOSCARNET.TM., and/or CIDOFOVIR.TM.. . .

L11 ANSWER 2 OF 17 USPATFULL on STN
AN 2003:112970 USPATFULL
TI Nucleic acids, proteins, and antibodies
IN Rosen, Craig A., Laytonsville, MD, UNITED STATES
Ruben, Steven M., Olney, MD, UNITED STATES
Barash, Steven C., Rockville, MD, UNITED STATES
PA Human Genome Sciences, Inc., Rockville, MD, UNITED STATES (U.S. corporation)
PI US 2003077703 A1 20030424
AI US 2002-73912 A1 20020214 (10)
RLI Continuation of Ser. No. US 2001-764862, filed on 17 Jan 2001, PENDING
PRAI US 2000-179065P 20000131 (60)
US 2000-180628P 20000204 (60)
US 2000-214886P 20000628 (60)
US 2000-217487P 20000711 (60)
US 2000-225758P 20000814 (60)
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US 2000-225267P 20000814 (60)
US 2000-216880P 20000707 (60)
US 2000-225270P 20000814 (60)

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US	2000-224518P	20000814 (60)
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US	2000-249218P	20001117 (60)
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US	2000-251479P	20001206 (60)
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US	2000-198123P	20000418 (60)

US 2000-227009P 20000823 (60)
US 2000-235484P 20000926 (60)
US 2000-190076P 20000317 (60)
US 2000-209467P 20000607 (60)
US 2000-205515P 20000519 (60)
US 2001-259678P 20010105 (60)
DT Utility
FS APPLICATION
LREP HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
CLMN Number of Claims: 24
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 17803
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to novel proteins. More specifically, isolated nucleic acid molecules are provided encoding novel polypeptides. Novel polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human polynucleotides and/or polypeptides, and antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to these novel polypeptides. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.
SUMM . . . adrenal adenoma adrenal gland
Bluescript SK-
L0373 NCI_CGAP_Col1 tumor colon
Bluescript SK-
L0375 NCI_CGAP_Kid6 kidney tumor kidney
Bluescript SK-
L0439 Soares infant brain ***INIB*** whole
biain Lafmid BA
L0517 NCI_CGAP_Pr1
pAMP10
L0518 NCI_CGAP_Pr2
pAMP10
L0586 HTCDL1
pBluesscript
SK(-)
L0589 Stratagene fetal retina
pBluescript SK-
937202
L0591 Stratagene HeLa cell. . .
SUMM . . . enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: Vibrio cholerae, ***Mycobacterium*** leprae, Salmonella typhi, Salmonella paratyphi, Meisseria meningitidis, Streptococcus pneurnoniae, Group B streptococcus, Shigella spp., Enterotoxigenic Escherichia coli, Enterohemorrhagic E. coli,. . .
SUMM . . . Yersinia, Shigella), Erysipelothrix, Haemophilus (e.g., Haemophilus influenza type B), Helicobacter, Legionella (e.g., Legionella pneumophila), Leptospira, Listeria (e.g., Listeria monocytogenes), Mycoplasma, ***Mycobacterium*** (e.g., ***Mycobacterium*** leprae and ***Mycobacterium*** tuberculosis),

Vibrio (e.g., Vibrio cholerae), Neisseriaceae (e.g., Neisseria gonorrhea, Neisseria meningitidis), Pasteurellacea, Proteus, Pseudomonas (e.g., Pseudomonas aeruginosa), Rickettsiaceae, Spirochetes (e.g.,. .
.

DETD . . . the invention are used in any combination with ISONIAZID.TM., RIFAMPIN.TM., PYRAZINAMIDE.TM., and/or ETHAMBUTOL.TM. to prophylactically treat or prevent an opportunistic ***Mycobacterium*** avium complex infection. In another specific embodiment, Therapeutics of the invention are used in any combination with RIFABUTIN.TM., CLARITHROMYCIN.TM., and/or AZITHROMYCIN.TM. to prophylactically treat or prevent an opportunistic ***Mycobacterium*** tuberculosis infection. In another specific embodiment, Therapeutics of the invention are used in any combination with GANCICLOVIR.TM., FOSCARNET.TM., and/or CIDOFOVIR.TM.. . .

L11 ANSWER.3 OF 17 USPATFULL on STN
AN 2003:86302 USPATFULL
TI Nucleic acids, proteins, and antibodies
IN Rosen, Craig A., Laytonsville, MD, UNITED STATES
Ruben, Steven M., Olney, MD, UNITED STATES
Barash, Steven C., Rockville, MD, UNITED STATES
PA Human Genome Sciences, Inc., Rockville, MD, UNITED STATES (U.S. corporation)
PI US 2003059908 A1 20030327
AI US 2002-91504 A1 20020307 (10)
RLI Continuation of Ser. No. US 2001-764869, filed on 17 Jan 2001, ABANDONED
PRAI US 2000-179065P 20000131 (60)
US 2000-180628P 20000204 (60)
US 2000-214886P 20000628 (60)
US 2000-217487P 20000711 (60)
US 2000-225758P 20000814 (60)
US 2000-220963P 20000726 (60)
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US 2000-225447P 20000814 (60)
US 2000-218290P 20000714 (60)
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US 2000-190076P 20000317 (60)
US 2000-209467P 20000607 (60)
US 2000-205515P 20000519 (60)
US 2001-259678P 20010105 (60)

DT Utility
FS APPLICATION
LREP HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
CLMN Number of Claims: 24
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 28555
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to novel cardiovascular system related

polynucleotides and the polypeptides encoded by these polynucleotides herein collectively known as "cardiovascular system antigens," and the use of such cardiovascular system antigens for detecting disorders of the cardiovascular system, particularly the presence of cancer of cardiovascular system tissues and cancer metastases. More specifically, isolated cardiovascular system associated nucleic acid molecules are provided encoding novel cardiovascular system associated polypeptides. Novel cardiovascular system polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human cardiovascular system associated polynucleotides and/or polypeptides. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to the cardiovascular system, including cancer of cardiovascular system tissues, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting the production and function of the polypeptides of the present invention.

SUMM . . . Bluescript SK-

L0378 NCI_CGAP_Lu1 lung tumor lung Bluescript SK-

L0438 normalized infant brain total brain brain lafmid BA cDNA

L0439 Soares infant brain ***INIB*** whole brain Lafmid BA

L0455 Human retina cDNA retina eye lambda gt10 randomly primed sublibrary

L0459 Adult heart, Clontech Lambda gt11

L0471 Human. . .

SUMM . . . enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: Vibrio cholerae, ***Mycobacterium*** leprae, Salmonella typhi, Salmonella paratyphi, Meisseria meninegitidis, Streptococcus pneumoniae, Group B streptococcus, Shigella spp., Enterotoxigenic Escherichia coli, Enterohemorrhagic E. Coli,. . .

SUMM . . . to, include, but not limited to, the following Gram-Negative and Gram-positive bacteria and bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, ***Mycobacterium*** , Norcardia), Cryptococcus neoformans, Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceac, Blastomycosis, Bordetella, Borrelia (e.g., Borrelia burgdorferi, Brucellosis, Candidiasis, Campylobacter, Coccidioidomycosis, Cryptococcosis,. . . Enterohemorrhagic E. coli), Enterobacteriaceae (Klebsiella, Salmonella (e.g., Salmonella typhi, and Salmonella paratyphi), Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, ***Mycobacterium*** leprae, Vibrio cholerae, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Menigococcal), Meisseria meningitidis, Pasteurellacea Infections (e.g., Actinobacillus, Heamophilus (e.g., Heamophilus influenza type B),. . .

DETD . . . the invention are used in any combination with ISONIAZID.TM., RIFAMPIN.TM., PYRAZINAMIDE.TM., and/or ETHAMBUTOL.TM. to prophylactically treat or prevent an opportunistic ***Mycobacterium***

avium complex infection. In another specific embodiment, Therapeutics of the invention are used in any combination with RIFABUTIN.TM., CLARITHROMYCIN.TM., and/or AZITHROMYCIN.TM. to prophylactically treat or prevent an opportunistic ***Mycobacterium*** tuberculosis infection. In another specific embodiment, Therapeutics of the invention are used in any combination with GANCICLOVIR.TM., FOSCARNET.TM., and/or CIDOFOVIR.TM.. . .

L11 ANSWER 4 OF 17 USPATFULL on STN
AN 2003:64784 USPATFULL
TI Nucleic acids, proteins, and antibodies
IN Rosen, Craig A., Laytonsville, MD, UNITED STATES
Ruben, Steven M., Olney, MD, UNITED STATES
Barash, Steven C., Rockville, MD, UNITED STATES
PA Human Genome Sciences, Inc., Rockville, MD, UNITED STATES, 20850 (U.S. corporation)
PI US 2003044905 A1 20030306
AI US 2002-73979 A1 20020214 (10)
RLI Continuation of Ser. No. US 2001-764885, filed on 17 Jan 2001, ABANDONED
PRAI US 2000-179065P 20000131 (60)
US 2000-180628P 20000204 (60)
US 2000-214886P 20000628 (60)
US 2000-217487P 20000711 (60)
US 2000-225758P 20000814 (60)
US 2000-220963P 20000726 (60)
US 2000-217496P 20000711 (60)
US 2000-225447P 20000814 (60)
US 2000-218290P 20000714 (60)
US 2000-225757P 20000814 (60)
US 2000-226868P 20000822 (60)
US 2000-216647P 20000707 (60)
US 2000-225267P 20000814 (60)
US 2000-216880P 20000707 (60)
US 2000-225270P 20000814 (60)
US 2000-251869P 20001208 (60)
US 2000-235834P 20000927 (60)
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US 2000-249299P 20001117 (60)
US 2000-236327P 20000929 (60)
US 2000-241785P 20001020 (60)
US 2000-244617P 20001101 (60)
US 2000-225268P 20000814 (60)
US 2000-236368P 20000929 (60)
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US 2000-251868P 20001208 (60)
US 2000-229344P 20000901 (60)
US 2000-234997P 20000925 (60)
US 2000-229343P 20000901 (60)
US 2000-229345P 20000901 (60)
US 2000-229287P 20000901 (60)

US	2000-229513P	20000905 (60)
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US	2000-229509P	20000905 (60)
US	2000-236367P	20000929 (60)
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US	2000-237038P	20001002 (60)
US	2000-236370P	20000929 (60)
US	2000-236802P	20001002 (60)
US	2000-237037P	20001002 (60)
US	2000-237040P	20001002 (60)
US	2000-240960P	20001020 (60)
US	2000-239935P	20001013 (60)
US	2000-239937P	20001013 (60)
US	2000-241787P	20001020 (60)
US	2000-246474P	20001108 (60)
US	2000-246532P	20001108 (60)
US	2000-249216P	20001117 (60)
US	2000-249210P	20001117 (60)
US	2000-226681P	20000822 (60)
US	2000-225759P	20000814 (60)
US	2000-225213P	20000814 (60)
US	2000-227182P	20000822 (60)
US	2000-225214P	20000814 (60)
US	2000-235836P	20000927 (60)
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US	2000-249244P	20001117 (60)
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US	2000-249211P	20001117 (60)
US	2000-249215P	20001117 (60)
US	2000-249264P	20001117 (60)
US	2000-249214P	20001117 (60)
US	2000-249297P	20001117 (60)
US	2000-232400P	20000914 (60)
US	2000-231242P	20000908 (60)
US	2000-232081P	20000908 (60)
US	2000-232080P	20000908 (60)
US	2000-231414P	20000908 (60)
US	2000-231244P	20000908 (60)
US	2000-233064P	20000914 (60)
US	2000-233063P	20000914 (60)
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US	2000-232399P	20000914 (60)
US	2000-232401P	20000914 (60)
US	2000-241808P	20001020 (60)
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US	2000-241221P	20001020 (60)
US	2000-246475P	20001108 (60)
US	2000-231243P	20000908 (60)

US 2000-233065P 20000914 (60)
US 2000-232398P 20000914 (60)
US 2000-234998P 20000925 (60)
US 2000-246477P 20001108 (60)
US 2000-246528P 20001108 (60)
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US 2000-246476P 20001108 (60)
US 2000-246526P 20001108 (60)
US 2000-249209P 20001117 (60)
US 2000-246527P 20001108 (60)
US 2000-246523P 20001108 (60)
US 2000-246524P 20001108 (60)
US 2000-246478P 20001108 (60)
US 2000-246609P 20001108 (60)
US 2000-246613P 20001108 (60)
US 2000-249300P 20001117 (60)
US 2000-249265P 20001117 (60)
US 2000-246610P 20001108 (60)
US 2000-246611P 20001108 (60)
US 2000-230437P 20000906 (60)
US 2000-251990P 20001208 (60)
US 2000-251988P 20001205 (60)
US 2000-251030P 20001205 (60)
US 2000-251479P 20001206 (60)
US 2000-256719P 20001205 (60)
US 2000-250160P 20001201 (60)
US 2000-251989P 20001208 (60)
US 2000-250391P 20001201 (60)
US 2000-254097P 20001211 (60)
US 2000-231968P 20000912 (60)
US 2000-226279P 20000818 (60)
US 2000-186350P 20000302 (60)
US 2000-184664P 20000224 (60)
US 2000-189874P 20000316 (60)
US 2000-198123P 20000418 (60)
US 2000-227009P 20000823 (60)
US 2000-235484P 20000926 (60)
US 2000-190076P 20000317 (60)
US 2000-209467P 20000607 (60)
US 2000-205515P 20000519 (60)
US 2001-259678P 20010105 (60)

DT Utility
FS APPLICATION
LREP HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
CLMN Number of Claims: 24
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 17010
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to novel proteins. More specifically, isolated nucleic acid molecules are provided encoding novel polypeptides. Novel polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human polynucleotides and/or polypeptides, and antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to these novel

polypeptides. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

SUMM . . . Uni-ZAP XR

S0222 H. Frontal cortex, epileptic, re-excision H. Brain, Frontal Cortex, Epileptic Brain disease Uni-ZAP XR

L0439 Soaies infant brain whole brain ***INIB*** Lafmid BA

L0581 Stratagene liver (#937224) pBluescript SK liver

L0761 NCI_CGAP_CLLI pT7T3D-Pac (Pharmacia) B-cell, chronic lymphotic leukemia with a modified

. . .

SUMM . . . enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: Vibrio cholerae, ***Mycobacterium*** leprae, Salmonella typhi, Salmonella paratyphi, Meisseria meningitidis, Streptococcus pneumoniae, Group B streptococcus, Shigella spp., Enterotoxigenic Escherichia coli, Enterohemorrhagic E. coli,. . .

SUMM . . . Yersinia, Sliigella), Erysipelothrix, Haemophilus (e.g., Haemophilus influenza type B), Helicobacter, Legionella (e.g., Legionella pneumophila), Leptospira, Listeria (e.g., Listeria monocytogenes), Mycoplasma, ***Mycobacterium*** (e.g., ***Mycobacterium*** leprae and ***Mycobacterium*** tuberculosis), Vibrio (e.g., Vibrio cholerae), Neisseriaceae (e.g., Neisseria gonorrhea, Neisseria meningitidis), Pasteurellacea, Proteus, Pseudomonas (e.g., Pseudomonas aeruginosa), Rickettsiaceae, Spirochetes (e.g.,. .

DETD . . . the invention are used in any combination with ISONIAZID.TM., RIFAMPIN.TM., PYRAZINAMIDE.TM., and/or ETHAMBUTOL.TM. to prophylactically treat or prevent an opportunistic ***Mycobacterium*** avium complex infection. In another specific embodiment, Therapeutics of the invention are used in any combination with RIFABUTIN.TM., CLARITHROMYCIN.TM., and/or AZITHROMYCIN.TM. to prophylactically treat or prevent an opportunistic ***Mycobacterium*** tuberculosis infection. In another specific embodiment, Therapeutics of the invention are used in any combination with GANCICLOVIR.TM., FOSCARNET.TM., and/or CIDOFOVIR.TM.. . .

L11 ANSWER 5 OF 17 USPATFULL on STN

AN 2002:314436 USPATFULL

TI Bacteriocin-containing sorbic acid product as addition to feedstuffs in agricultural livestock rearing

IN Raczek, Nico N., Kelkheim, GERMANY, FEDERAL REPUBLIC OF

PI US 2002176910 A1 20021128

AI US 2002-80198 A1 20020219 (10)

PRAI DE 2001-110431 20010305

DT Utility

FS APPLICATION

LREP ProPat, L.L.C., 2912 Crosby Road, Charlotte, NC, 28211-2815

CLMN Number of Claims: 13
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 478
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to a product for use in animal feedstuffs. The product comprises sorbic acid and live or dead microorganisms which secrete bacteriocins, or the bacteriocins themselves or combinations thereof and, where appropriate, a carrier. The invention further relates to the use of the product on its own in feedstuffs or in a mixture with other feed additives for improving the hygienic status of the feed and for improving performance in agricultural livestock rearing.
SUMM . . . nisin, reuterin
Clostridium perfringens nisin, pediocin-A, pediocin-AcH, pediocin-VTT, reuterin, thermophillin
Clostridium sporogens nisin, pediocin-A
Clostridium tyrobutricum lacticin-481, lactocin-S, pediocin-AcH
Enterococcus faecalis
Enterococcus faecalis 226, ***INIA*** 4 enterocin 226NWC, AS-48
Enterococcus faecalis S-48 bacteriocin Bc-48
Enterococcus faecium, BFE 900, enterocin 1146, B, A, Cal, ON- 157,
CTC492, cal 1,. . . leucocin-A, nisin, pediocin-A, pediocin AcH, pediocin-JD, pediocin-PA-1, pediocin-PAC10, pediocin-VVT, piscicolin-61, reuterin, sakacin-A, sakacin-P
Listeria seeligeri pediocin-A
Listeria welchii lacticin-481, pediocin-A
Mycobacterium tuberculosis nisin
Pediococcus acidilactic e.a. H, E, F, M pediocin AcH
Pediococcus acidilactic JD1-23, PAC 1.0, SJ-1, pediocin JD, PA-1, SJ-1
Pediococcus pentosaceus pediocin A,. . .
CLM What is claimed is:
. . . nisin, reuterin
Clostridium perfringens nisin, pediocin-A, pediocin-AcH, pediocin-VTT, reuterin, thermophillin
Clostridium sporogens nisin, pediocin-A
Clostridium tyrobutricum lacticin-481, lactocin-S, pediocin-AcH
Enterococcus faecalis
Enterococcus faecalis 226, ***INIA*** 4 enterocin 226NWC, AS-48
Enterococcus faecalis S-48 bacteriocin Bc-48
Enterococcus faecium, BFE 900, enterocin 1146, B, A, Cal, ON- 157,
CTC492, cal 1,. . . lactacin-B, lacticin-481, leucocin-A, nisin, pediocin-A, pediocin AcH, pediocin-JD, pediocin-PA-1, pediocin-PAC10, pediocin-VVT, piscicolin-61, reuterin, sakacin-A, sakacin-P
Listeria seeligeri pediocin-A
Listeria welchii lacticin-481, pediocin-A
Mycobacterium tuberculosis nisin
Pediococcus acidilactic e.a. H, E, F, M pediocin AcH

Pediococcus acidilactic JD1-23, pediocin JD, PA-1, SJ-1
PAC 1.0, SJ-1,
Pediococcus pentosaceus pediocin A,. . .

L11 ANSWER 6 OF 17 USPATFULL on STN
AN 2002:272887 USPATFULL
TI ***IniB*** , ***iniA*** and ***iniC*** genes of ***mycobacteria*** and methods of use
IN Alland, David, Dobbs Ferry, NY, UNITED STATES
Bloom, Barry R., Hastings-on-Hudson, NY, UNITED STATES
Jacobs, William R., JR., City Island, NY, UNITED STATES
PI US 2002151008 A1 20021017
AI US 2001-918951 A1 20010731 (9)
RLI Continuation of Ser. No. US 1998-177349, filed on 23 Oct 1998, PATENTED
DT Utility
FS APPLICATION
LREP Elie H. Gendloff, Ph.D., Esq., AMSTER, ROTHSTEIN & EBENSTEIN, 90 Park Avenue, New York, NY, 10016
CLMN Number of Claims: 47
ECL Exemplary Claim: 1
DRWN 10 Drawing Page(s)
LN.CNT 935
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to the identification, cloning, sequencing and characterization of the ***iniB*** , ***iniA*** and ***iniC*** genes of ***mycobacteria*** which are induced by a broad class of antibiotics that act by inhibiting cell wall biosynthesis, including the first line antituberculosis agents, isoniazid and ethambutol. The present invention provides purified and isolated ***iniB*** , ***iniA*** , ***iniC*** and ***iniB*** promoter nucleic acids which may comprise the iniBAC operon, as well as mutated forms of these nucleic acids. The present invention also provides one or more single-stranded nucleic acid probes which specifically hybridize to the ***iniB*** , ***iniA*** , ***iniC*** and ***iniB*** promoter
nucleic acids, and mixtures thereof, which may be formulated in kits, and used in the diagnosis of drug-resistant ***mycobacterial*** strain. The present invention also provides methods for the screening and identification of drugs effective against ***Mycobacterium*** tuberculosis using induction of the ***iniB*** promoter.
TI ***IniB*** , ***iniA*** and ***iniC*** genes of ***mycobacteria*** and methods of use
AB This invention relates to the identification, cloning, sequencing and characterization of the ***iniB*** , ***iniA*** and ***iniC*** genes of ***mycobacteria*** which are induced by a broad class of antibiotics that act by inhibiting cell wall biosynthesis, including the first line antituberculosis agents, isoniazid and ethambutol. The present invention provides purified and isolated ***iniB*** , ***iniA*** , ***iniC*** and ***iniB*** promoter nucleic acids which may comprise the iniBAC operon, as well as mutated forms of these nucleic acids. The present invention also provides one or more single-stranded nucleic acid probes which specifically hybridize to the ***iniB*** , ***iniA*** , ***iniC*** and ***iniB*** promoter
nucleic acids, and mixtures thereof, which may be formulated in kits, and used in the diagnosis of drug-resistant ***mycobacterial*** strain. The present invention also provides methods for the screening

and identification of drugs effective against ***Mycobacterium*** tuberculosis using induction of the ***iniB*** promoter.

SUMM [0001] This invention is based upon the discovery by the inventors of the ***iniB*** , ***iniA*** and ***iniC*** genes, and the proteins encoded by these genes which are induced by a broad class of antibiotics that act by inhibiting cell wall biosynthesis, including the first line antituberculosis agents, isoniazid (INH) and ethambutol (EMB). The discovery of the ***iniB*** , ***iniA*** and ***iniC*** genes, and the proteins encoded by these genes will have important implications in the identification of drugs effective against M. tuberculosis, as well as the treatment of drug-resistant ***mycobacterial*** strains.

SUMM [0004] EMB targets the ***mycobacterial*** cell wall, a unique structure among prokaryotes which consists of an outer layer of mycolic acids covalently bound to peptidoglycan. . .

SUMM . . . aid in screening for new drugs. This would require the identification of genes that participate in the biosynthesis of the ***mycobacterial*** cell wall and the identification of mutants of these genes encoding proteins that confer resistance to drugs. While it is possible that the ***iniB*** , ***iniA*** , and ***iniC*** gene products are not in themselves targets for currently available antibiotics, these proteins may act to protect M. tuberculosis and other ***mycobacteria*** from toxic effects that occur when cell wall biosynthesis is inhibited by antibiotics. Novel drugs that inhibit the ***iniB*** , ***iniA*** , and ***iniC*** proteins may therefore act synergistically with other cell wall active antibiotics and prove useful in treating tuberculosis, including drug resistant. . .

SUMM [0010] The present invention is directed to the nucleic acid sequences of the ***iniB*** , ***iniA*** and ***iniC*** genes, and the proteins encoded by these genes which are induced by a broad class of antibiotics that act by. . .

SUMM [0012] The present invention specifically provides purified and isolated nucleic acid sequences of the ***iniB*** , ***iniA*** , and ***iniC*** genes, as well as mutated forms of these genes. The present invention also provides one or more single-stranded nucleic acid probes which specifically hybridize to the nucleic acid sequences of the ***iniB*** , ***iniA*** , and ***iniC*** genes, as well as mutated forms of these genes, and mixtures thereof, which may be formulated in kits, and used in the detection of drug resistant ***mycobacterial*** strains.

SUMM [0013] The present invention also provides purified active ***iniB*** , ***iniA*** , and ***iniC*** proteins encoded by the ***iniB*** , ***iniA*** , and ***iniC*** genes. Also provided are antibodies immunoreactive with the protein(s) expressed by the ***iniB*** , ***iniA*** , and ***iniC*** genes, and analogues thereof, as well as antibodies immunoreactive with the protein(s) expressed by the these genes.

SUMM . . . present invention is a method of screening drugs or compounds to determine whether the drug or compound is effective against ***Mycobacterium*** tuberculosis.

DRWD [0016] FIG. 1: FIG. 1 shows induction of the ***iniA*** gene after treatment with different antibiotics. Autoradiographs of a Northern blot containing RNA from M. tuberculosis cultures treated either with. . . isoniazid 1 .mu.g/ml; ethambutol 5 .mu.g/ml; streptomycin 5 .mu.g/ml; and rifampin 5 .mu.g/ml. The blots were hybridized first with an ***iniA*** DNA probe (top) to examine ***iniA*** induction; the

blot was then stripped and re-hybridized with a 16S probe (bottom) to confirm equal RNA loading.

DRWD . . . was equalized by comparison of the 16S band intensity. RT PCR using three ten-fold dilutions of each RNA and either ***iniA*** , asd or 16S specific primers was performed. Induction of ***iniA*** and suppression of asd by isoniazid is demonstrated. The amount of 16S RT PCR product is similar for equivalent dilutions,. . . of starting RNA. Lanes 7-8 are minus RT controls; and lane 9 a negative PCR control. FIG. 2B: Lack of ***iniA*** induction in an isoniazid resistant strain. Cultures of isogenic BCG strain ATCC35735 which is susceptible to isoniazid (lanes 1-6), or. . . for the last 18 hours. Three ten-fold dilutions of RNA extracted from each culture were tested by RT PCR for ***iniA*** induction. Induction is seen only in the INH susceptible strain. Lanes 13-16 are minus RT controls; and lane 17 a. .

.

DRWD [0018] FIG. 3: FIG. 3 shows the results of the experiments directed to the induction of the ***iniB*** promoter.

DRWD [0019] FIG. 4: FIG. 4 shows the results of the experiments directed to the induction of ***iniB*** by amino acids.

DRWD [0020] FIG. 5: FIG. 5 shows the results of the experiments directed to the induction of the ***iniB*** promoter as a function of growth phase.

DRWD [0021] FIGS. 6A-6C: FIGS. 6A-6C set forth the nucleic acid sequences of the ***iniB*** , ***iniA*** and ***iniC*** genes, and the promoter region of the ***iniB*** gene. MTCY279, genebank accession Z97991. Nucleotides 9048-9101, then nucleotides 1-159 of M. tuberculosis cosmid MTY13E10, genebank accession Z95324. For a total of 213 nucleotides. Nucleotide sequences of genes, numbering from MTY13E10iniB 160-1559; ***iniA*** 1636-3558 and ***iniC*** 3555-5036.

DRWD [0022] FIG. 7: FIG. 7 sets forth the amino acid sequences encoded by the ***iniB*** , ***iniA*** , and ***iniC*** genes.

DETD [0023] The present invention is directed to the nucleic acid sequences of the ***iniB*** , ***iniA*** and ***iniC*** genes, and the proteins encoded by these genes which are induced by a broad class of antibiotics that act by. . .

DETD [0024] The present invention specifically provides purified and isolated nucleic acid sequences of the ***iniB*** , ***iniA*** , ***iniC*** and ***iniB*** promoter genes. Also provided are mutated forms of these nucleic acids. It is possible, that the ***iniB*** , ***iniA*** and ***iniC*** genes may form an operon, herein designated the "iniBAC operon" or the " ***iniA*** operon". As used herein, an "operon" is a cluster of related genes and their promoters that encode for open reading frames. The "iniBAC operon" as used herein consists of the ***iniB*** , ***iniA*** and ***iniC*** genes arranged in a single operon, as well as the sequences encoding the promoters for the iniBAC genes. The "wild type miniBAC operon" is herein defined as the normal form of the ***iniB*** , ***iniA*** , and ***iniC*** genes which express gene products, and includes degenerate forms. The "mutated iniBAC operon" is the mutated form of the normal. . . herein, "nucleic acid" may be genomic DNA, cDNA or RNA, and may be the entire nucleic acid sequence comprising the ***iniB*** , ***iniA*** , and ***iniC*** genes, the nucleic acid sequence of the ***iniB*** gene and its promoter, the nucleic acid sequence of the ***iniB*** promoter, or any portion of the sequence thereof.

DETD [0025] The present invention specifically provides for the ***iniB*** , ***iniA*** , and ***iniC*** nucleic acid sequences isolated from M. tuberculosis. These sequences are set forth in FIG. 6. The present invention also provides for the ***iniB*** , ***iniA*** , and ***iniC*** nucleic acid sequences which encodes the amino acid sequence set forth in FIG. 7. The present invention provides for the nucleic acid sequence comprising the ***iniB*** promoter region set forth in FIG. 6. FIG. 6 indicates the position of the ***iniB*** promoter, however, it is to be understood that the ***iniB*** promoter may consist of additional nucleotides upstream from the ***iniB*** promoter region indicated in FIG. 6.

DETD [0026] The present invention further provides for mutated nucleic acid sequences of the ***iniB*** , ***iniA*** , and ***iniC*** nucleic acid sequences. These mutation(s) may be deletions, insertions, substitutions, missense, nonsense, point or rearrangement mutations, or a combination thereof.

DETD [0027] The nucleic acid sequences of the ***iniB*** , ***iniA*** , and ***iniC*** genes can be prepared several ways. For example, they can be prepared by isolating the nucleic acid sequences from a natural source, or by synthesis using recombinant DNA techniques. In addition, mutated nucleic acid sequences of the ***iniB*** , ***iniA*** , and ***iniC*** genes can be prepared using site mutagenesis techniques. The amino acid sequences may also be synthesized by methods commonly known. . .

DETD . . . nucleic acid probes and mixtures thereof for use in detecting drug resistance caused by a mutated nucleic acid of the ***iniB*** , ***iniA*** , or ***iniC*** genes. The nucleic acid probes may be DNA, cDNA, or RNA, and may be prepared from the mutated and/or wild type nucleic acid sequences comprising the ***iniB*** , ***iniA*** , or ***iniC*** genes. The probes may be the full length sequence of the nucleic acid sequences comprising the ***iniB*** , ***iniA*** , or ***iniC*** genes, or fragments thereof. Typical probes are 12 to 40 nucleotides in length. The probes may be synthesized using an. . . including .sup.32P and biotin, and the like. Combinations of two or more labeled probes corresponding to different regions of the ***iniB*** , ***iniA*** , or ***iniC*** genes also may be included in kits to allow for the detection and/or analysis of the ***iniB*** , ***iniA*** , and ***iniC*** genes by hybridization.

DETD [0029] Specifically, the nucleic acid sequences of the ***iniB*** , ***iniA*** , or ***iniC*** genes may be used to produce probes which can be used in the identification, treatment and prevention of diseases caused by microorganisms and to determine whether various drugs are effective against ***mycobacterial*** strains.

DETD [0030] The present invention also provides purified active ***iniB*** , ***iniA*** , and ***iniC*** proteins, encoded by the ***iniB*** , ***iniA*** , and ***iniC*** genes. The proteins may be expressed by the wild type or mutated nucleic acid sequences of the ***iniB*** , ***iniA*** , and ***iniC*** genes, or an analogue thereof. As used herein, "analogue" means functional variants of the wild type protein, and includes ***iniB*** , ***iniA*** , and ***iniC*** proteins isolated from bacterial sources other then ***mycobacteria*** , as well as functional variants thereof. The proteins may also be isolated from native cells, or recombinantly produced.

DETD [0031] The present invention also provides antibodies immunoreactive with the proteins expressed by the ***iniB*** , ***iniA*** , and

iniC genes, and analogues thereof, as well as antibodies immunoreactive with the proteins expressed by the mutated nucleic acid sequences of the ***iniB*** , ***iniA*** , and ***iniC*** genes. The antibodies may be polyclonal or monoclonal and are produced by standard techniques. The antibodies may be labeled with. . . standard detectable markers (e.g. chemiluminescent detection systems and radioactive labels such as .sup.125I) for detecting the wild type and mutated ***iniB*** , ***iniA*** , and ***iniC*** genes. The antibodies may also be presented in kits with detectable labels and other reagents and buffers for such detection.

DETD [0032] The present invention also provides for a method of assessing the susceptibility of a ***mycobacterium*** to EMB and/or isoniazid in a clinical sample comprising isolating the ***mycobacterial*** chromosomal DNA from a clinical sample, preparing oligonucleotides utilizing the wild-type or mutant ***iniB*** , ***iniA*** , or ***iniC*** nucleic acid sequences, amplifying the region of the ***iniB*** , ***iniA*** , or ***iniC*** gene from the clinical sample, and determining whether a mutated ***iniB*** , ***iniA*** , or ***iniC*** gene exists in the ***mycobacterial*** strain in the clinical sample.

DETD [0033] The ***mycobacteria*** that may be assessed by this method of the present invention include, but are not limited to, ***Mycobacterium*** tuberculosis, ***Mycobacterium*** avium, ***Mycobacterium*** smegmatis, ***Mycobacterium*** bovis BCG, ***Mycobacterium*** leprae, ***Mycobacterium*** africanum, and ***Mycobacterium*** intracellulare.

DETD [0035] The present invention also provides for a method of treating a ***mycobacterial*** infection in a subject by obtaining anti-DNA or anti-RNA nucleic acid sequences capable of inhibiting the mRNA activity of the ***iniB*** , ***iniA*** , or ***iniC*** genes of a ***mycobacterium*** , utilizing a wild type or the mutant nucleic acid of the ***iniB*** , ***iniA*** , or ***iniC*** genes, and administering an amount of said nucleic acid sequences, either alone or in combination with other compositions to treat the ***mycobacterial*** infection in a subject.

DETD . . . anti-DNA or anti-RNA nucleic acid sequences employed in the method may be mutant or wild-type nucleic acid sequences of the ***iniB*** , ***iniA*** , or ***iniC*** genes. The mutant nucleic acid sequence may contain one or more deletions, insertions, substitutions, missense, nonsense, polymorphisms, point, or rearrangement. . .

DETD [0037] Non-limiting examples of infections that can be treated using the methods of the present invention include those caused by ***mycobacteria*** selected from the group consisting of ***Mycobacterium*** tuberculosis, ***Mycobacterium*** avium, ***Mycobacterium*** smegmatis, ***Mycobacterium*** bovis BCG, ***Mycobacterium*** leprae, ***Mycobacterium*** africanum, and ***Mycobacterium*** intracellulare.

DETD . . . used herein, "subject" may be an embryo, fetus, newborn, infant, or adult. Further, as used herein "treating" is contacting a ***mycobacterium*** with the nucleic acids of the present invention, alone or in combination with other compositions.

DETD [0039] The present invention additionally provides for the use of the nucleic acid sequences of the ***iniB*** , ***iniA*** , or ***iniC*** genes of the present invention as vaccines, or to improve existing vaccines.

DETD [0040] Non-limiting examples of ***mycobacterial*** infections that

can be treated using the vaccines of the present invention include those caused by ***mycobacteria*** selected from the group consisting of ***Mycobacterium*** tuberculosis, ***Mycobacterium*** avium, ***Mycobacterium*** smegmatis, ***Mycobacterium*** bovis BCG, ***Mycobacterium*** leprae, ***Mycobacterium*** africanum, and ***Mycobacterium*** intracellulare. For example, M. tuberculosis complex strains that have mutations in the ***iniB*** , ***iniA*** or ***iniC*** genes might have reduced virulence. In addition, mutated genes of M. tuberculosis and M. bovis can be added to BCG. . .

DETD . . . methods of using the constructs for screening drugs or compounds to determine whether the drug or compound is effective against ***Mycobacterium*** tuberculosis.

DETD [0042] Specifically provided by the present invention are vector constructs comprising a DNA sequence comprising the ***iniB*** promoter region. The DNA encoding the ***iniB*** promoter region may be obtained several ways. For example, it can be prepared by isolating the ***iniB*** promoter region DNA sequences from a natural source, by synthesis using recombinant DNA techniques, by synthesis using a DNA synthesizer,. . . or by amplification using the polymerase chain reaction. Such vectors may be constructed by inserting the DNA sequence comprising the ***iniB*** promoter region into a suitable vector. The term "inserted" as used herein means the ligation of a foreign DNA fragment. . .

DETD [0043] Vectors suitable for expression of a DNA sequence comprising the ***iniB*** promoter region in a cell are well known to those skilled in the art and include pQE-8 (Qiagen), pET-3d (Novagen),. . .

DETD . . . constructs will contain the necessary start, termination, ribosomal binding sequences, and control sequences for proper transcription and processing of the ***iniB*** promoter region when the vector construct is introduced into a host cell.

DETD . . . limited to, luciferase from Vibrio or of firefly origin; green fluorescent protein; beta-galactosidase; beta-glucoronidase; or catechol dehydrogenase and a strong ***mycobacterial*** promoter which controls expression of the reporter molecule-encoding gene. The reporter gene may be part of an existing vector, or. . .

DETD . . . In a preferred embodiment of the invention, the cell transformed with the vector construct of the present invention is a ***mycobacterium*** . Non-limiting examples of ***mycobacterium*** which may be transformed with the vector construct of the present invention are ***Mycobacterium*** tuberculosis, ***Mycobacterium*** avium, ***Mycobacterium*** smegmatis, ***Mycobacterium*** bovis BCG, ***Mycobacterium*** leprae, ***Mycobacterium*** africanum, and ***Mycobacterium*** intracellulare.

DETD [0051] The present invention also provides for the use of the vector constructs containing a DNA sequence comprising the ***iniB*** promoter region for screening drugs or compounds to determine whether the drug or compound is effective against ***Mycobacterium*** tuberculosis. This method comprises transforming the vector construct into a ***mycobacterium*** . Non-limiting examples of ***mycobacteria*** which may be used in this method include ***Mycobacterium*** tuberculosis, ***Mycobacterium*** avium, ***Mycobacterium*** smegmatis, ***Mycobacterium*** bovis BCG, ***Mycobacterium*** leprae, ***Mycobacterium*** africanum, and ***Mycobacterium*** intracellulare. The ***mycobacterium*** is cultured, preferably to an OD of 0.2-0.8. The drug or compound to be tested is then added to the culture and the ***mycobacteria*** are

allowed to grow further. After a determined period of time, the culture is measured for induction of the ***iniB*** promoter. Induction is preferably determined by the expression of a reporter gene, such as lacZ or luciferase. Induction of the ***iniB*** promoter is a positive indication of the effectiveness of the drug or compound against the ***Mycobacterium*** tuberculosis cell wall and any other mechanism to be determined.

DETD Isolation and Identification of the ***iniB*** , ***iniA*** , and ***iniC*** Genes

DETD [0055] RNA extraction. ***Mycobacterial*** cultures were grown to mid log phase in Middlebrook 7H9 media supplemented with OADC, 0.05% Tween 80, and cyclohexamide (18). . .

DETD . . . One microgram of RNA was reverse transcribed using the appropriate reverse PCR primer and superscript II at 50.degree. C. For ***iniA*** and asd, three serial ten-fold dilutions of cDNA were made;

16S cDNA was diluted 1 in 10.sup.6, 1 in 10.sup.7,. . . with Taq polymerase and 1.times.PCR buffer (Gibco BRL) containing 2 mM MgCl.sub.2 for 25 cycles annealing at 60.degree. C. for ***iniA*** ; 35 cycles annealing at 58.degree. C. for asd; 25 cycles annealing at 63.degree. C. for 16S. PCR products were analyzed. . . the amounts of PCR product were calculated by densitometry (Imaging Software, National Institute of Health, Bethesda, Md.). Primers used for ***iniA*** :

Primers used for ***iniA*** : 5'-GCGCTGGCGGGAGATCGTCAATG-3', 5'-TGGGCAGTCGGGTCACAGGAGTCG-3';

for asd: 5'-TCCCGCCGCCGAACACCTA-3', 5-GGATCCGGCCGACCAGAGA-3';

for 1 6 S : 5 ' - G G A G T. . .

DETD [0061] Induction of the ***iniB*** promoter. The 213 base pair ***iniB*** promoter region was cloned into a lacZ and fflux reporter construct and transformed into BCG. Cells were cultured to an. . .

DETD [0062] Induction of the ***iniB*** promoter by amino acids that block cell wall synthesis. D-threonine, but not L-threonine inhibits cell wall biosynthesis by disrupting D-ala/D-ala cross-linking of the peptidoglycan cell wall. BCG containing the ***iniB*** /lacZ construct were treated with various antibiotics and amino acids. Induction of the ***iniB*** promoter at 24 hours with D-threonine is comparable to that of isoniazid and Unisyn (amoxicillin/sulbactam). Modest induction is also seen with 1% gylcine which is also known to weaken the ***mycobacterial*** cell wall. However, the L-threonine control did not cause induction.

DETD [0063] Induction of the ***iniB*** promoter as a function of growth phase. One BCG culture containing the ***iniA*** /lacZ construct was diluted in media to an OD590 of less than 0.1. The culture was placed at 37.degree. C. with. . .

DETD [0064] Use of the ***iniB*** promoter to screen compounds for new cell wall active drugs. ***Mycobacteria*** , preferably M. tuberculosis but also other ***mycobacteria*** are transformed with a reporter construct under the control of the ***iniA*** promoter sequence as set forth in FIG. 6 or a smaller portion of this sequence, or a larger sequence. These. . . be assayed for activity of the reporter molecule preferably luciferase or beta galactosidase. Compounds that caused significant induction of the ***iniB*** promoter would be identified by comparing the reporter activity in the wells containing

the compounds to control wells to which. . .

DETD . . . frame that appeared to be the second gene of a probable three gene operon. This open reading frame was named ***iniA*** (isoniazid induced gene A), and the upstream open reading frame Rv0341, was named ***iniB*** . P2 encoded a sequence that was not complementary to P1, but that was identical to the third gene in the same probable operon Rv0343, this open reading frame was named ***iniC*** . A putative protein encoded by the ***iniA*** gene was found to contain a phosphopantetheine attachment site motif (21) suggesting that it functions as an acyl carrier protein. Both ***iniA*** and ***iniC*** lacked significant homology to other known genes but were 34% identical to each other. A sequence similarity search demonstrated that ***iniB*** had weak homology to alanine-glycine rich cell wall structural proteins (22). Northern blot analysis using excised inserts to probe total RNA from M. tuberculosis cultured in the presence or absence or different antibiotics verified that ***iniA*** was strongly induced by isoniazid and ethambutol, drugs that act by inhibiting cell wall biosynthesis but not by rifampin or. . .

DETD [0068] Reverse transcription (RT) PCR assays confirmed differential gene expression of both asd and ***iniA*** (FIG. 2A), as well as of ***iniB*** and ***iniC*** (data not shown). As predicted, ***iniA*** was strongly induced by isoniazid (70 fold induction by densitometry), while asd was repressed (17 fold). Induction of ***iniA*** was also tested in two isogenic strains of BCG that were either sensitive or resistant to isoniazid. The resistant phenotype. . . conferred by a mutation in katG which normally converts isoniazid from a prodrug to its active form (23). Induction of ***iniA*** was seen only in the susceptible BCG strain demonstrating the requirement for isoniazid activation.

DETD [0070] A three gene operon (the ***iniA*** operon) was discovered in M. tuberculosis that was strongly induced by both isoniazid and ethambutol. A 213 base pair sequence containing the ***iniB*** promoter was cloned into a lacZ reporter construct. Using this construct, it is herein demonstrated that the ***iniB*** promoter is induced by a wide range of cell wall active compounds but not by antibiotics or other stresses that do not act on the cell wall (FIG. 3 and FIG. 5). The ***iniB*** promoter is induced by antibiotics that act on very different targets within the cell wall including isoniazid which inhibits mycolic. . . which inhibits arabinan and lipoarabinomannan biosynthesis, cycloserine which inhibits peptidoglycan cross linking and amoxicillin/sulbactam which inhibits penicillin binding proteins. The ***iniA*** gene is also induced by D-threonine, an amino acid that substitutes for D-alanine and inhibits peptidoglycan biosynthesis. In contrast, L-threonine has a minimal effect on ***iniA*** transcription (FIG. 4). The induction is not an artifact of cell wall breakdown and increased release of the .mu.-galactosidase reporter because ***iniB*** promoter induction can be reversed by co-administration of the RNA polymerase inhibitor rifampin (FIG. 3). Induction has been demonstrated only. . . promoter but may also reflect the mechanisms of action of the antibiotics available for testing. It is possible that the ***iniA*** promoter is also inducible in stationary phase. This hypothesis would need to be tested with a compound that was able. . .

DETD [0071] The ***iniB*** promoter may be used in a reporter construct to rapidly screen compounds for new cell wall active drugs. Screening for ***iniB*** promoter induction would also permit drugs to be assayed at higher than normal concentrations because it will be possible

to distinguish between cell wall activity and nonspecific effects on cell growth. If the ***iniB*** promoter is inducible during stationary phase, then this strategy could be used to discover drugs that could be effective on. . .

CLM What is claimed is:

1. A purified and isolated nucleic acid sequence of the ***iniA*** gene.

6. A single-stranded nucleic acid probe which specifically hybridizes to a nucleic acid sequence of the ***iniA*** gene.

9. A purified, active protein encoded by the ***iniA*** gene.

12. An antibody immunoreactive with a protein encoded by the ***iniA*** gene.

13. The antibody of claim 12 which is immunoreactive with a wild type or mutated ***iniA*** protein.

15. A purified and isolated nucleic acid sequence of the ***iniB*** gene.

20. A single-stranded nucleic acid probe which specifically hybridizes to a nucleic acid sequence of the ***iniA*** gene.

23. A purified, active protein encoded by the ***iniB*** gene.

26. An antibody immunoreactive with a protein encoded by the ***iniB*** gene.

27. The antibody of claim 26 which is immunoreactive with a wild type or mutated ***iniB*** protein.

29. A purified and isolated nucleic acid sequence of the ***iniC*** gene.

34. A single-stranded nucleic acid probe which specifically hybridizes to a nucleic acid sequence of the ***iniC*** gene.

37. A purified, active protein encoded by the ***iniC*** gene.

40. An antibody immunoreactive with a protein encoded by the ***iniC*** gene.

41. The antibody of claim 40 which is immunoreactive with a wild type or mutated ***iniC*** protein.

43. A vector construct comprising the nucleotide sequence of the ***iniB*** promoter inserted into a plasmid.

46. A method of determining whether a drug is effective against ***Mycobacterium*** tuberculosis comprising: (a) transforming a vector construct comprising the nucleotide sequence 6f the ***iniB*** promoter inserted into a plasmid into a ***mycobacterium*** ; (b) culturing the ***mycobacterium*** ; (c) treating the cultured cells with the drug; and (d) measuring induction of the ***iniA*** promoter, the presence of induction indicating the drug is effective

against ***Mycobacterium*** tuberculosis.

L11 ANSWER 7 OF 17 USPATFULL on STN
AN 2002:171925 USPATFULL
TI Nucleic acids, proteins, and antibodies
IN Rosen, Craig A., Laytonsville, MD, UNITED STATES
Ruben, Steven M., Olney, MD, UNITED STATES
Barash, Steven C., Rockville, MD, UNITED STATES
PI US 2002090674 A1 20020711
AI US 2001-764903 A1 20010117 (9)
PRAI US 2000-179065P 20000131 (60)
DT Utility
FS APPLICATION
LREP HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
CLMN Number of Claims: 24
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 21376
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to novel respiratory system related polynucleotides and the polypeptides encoded by these polynucleotides herein collectively known as "respiratory system antigens," and the use of such respiratory system antigens for detecting disorders of the respiratory system, particularly the presence of cancer of respiratory system tissues and cancer metastases. More specifically, isolated respiratory system associated nucleic acid molecules are provided encoding novel respiratory system associated polypeptides. Novel respiratory system polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human respiratory system associated polynucleotides and/or polypeptides. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to the respiratory system, including cancer of respiratory system tissues, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting the production and function of the polypeptides of the present invention.
SUMM . . . Bluescript SK-
L0418 b4HB3MA-Cot109 + 10-
Lafmid BA
Bio
L0438 normalized infant brain total brain brain
lafmid BA
cDNA
L0439 Soares infant brain ***INIB*** whole
brain Lafmid BA
L0456 Human retina cDNA retina eye
lambda gt10
Tsp5091-cleaved
sublibrary
L0471 Human fetal heart,
Lambda ZAP
Lambda ZAP. . .
SUMM . . . enhance an immune response to a bacteria or fungus, disease, or

symptom selected from the group consisting of: Vibrio cholerae, ***Mycobacterium*** leprae, Salmonella typhi, Salmonella paratyphi, Meisseria meningitidis, Streptococcus pneumoniae, Group B streptococcus, Shigella spp., Enterotoxigenic Escherichia coli, Enterohemorrhagic E. coli,. . .

SUMM . . . Yersinia, Shigella), Erysipelothrix, Haemophilus (e.g., Haemophilus influenza type B), Helicobacter, Legionella (e.g., Legionella pneumophila), Leptospira, Listeria (e.g., Listeria monocytogenes), Mycoplasma, ***Mycobacterium*** (e.g., ***Mycobacterium*** leprae and ***Mycobacterium*** tuberculosis), Vibrio (e.g., Vibrio cholerae), Neisseriaceae (e.g., Neisseria gonorrhea, Neisseria meningitidis), Pasteurellacea, Proteus, Pseudomonas (e.g., Pseudomonas aerliginosa), Rickettsiaceae, Spirochetes (e.g.,. . .

DETD . . . the invention are used in any combination with ISONIAZID.TM., RIFAMPIN.TM., PYRAZINAMIDE.TM., and/or ETHAMBUTOL.TM. to prophylactically treat or prevent an opportunistic ***Mycobacterium*** avium complex infection. In another specific embodiment, Therapeutics of the invention are used in any combination with RIFABUTIN.TM., CLARITHROMYCIN.TM., and/or AZITHROMYCIN.TM. to prophylactically treat or prevent an opportunistic ***Mycobacterium*** tuberculosis infection. In another specific embodiment, Therapeutics of the invention are used in any combination with GANCICLOVIR.TM., FOSCARNET.TM., and/or CIDOFOVIR.TM.. . .

L11 ANSWER 8 OF 17 USPATFULL on STN
AN 2002:165192 USPATFULL
TI Nucleic acids, proteins, and antibodies
IN Rosen, Craig A., Laytonsville, MD, UNITED STATES
Ruben, Steven M., Olney, MD, UNITED STATES
Barash, Steven C., Rockville, MD, UNITED STATES
PI US 2002086821 A1 20020704
US 2003125246 A9 20030703
AI US 2001-764881 A1 20010117 (9)
PRAI US 2000-179065P 20000131 (60)
DT Utility
FS APPLICATION
LREP HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
CLMN Number of Claims: 24
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 27531
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to novel respiratory system related polynucleotides and the polypeptides encoded by these polynucleotides herein collectively known as "respiratory system antigens," and the use of such respiratory system antigens for detecting disorders of the respiratory system, particularly the presence of cancer of respiratory system tissues and cancer metastases. More specifically, isolated respiratory system associated nucleic acid molecules are provided encoding novel respiratory system associated polypeptides. Novel respiratory system polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human respiratory system associated polynucleotides and/or polypeptides. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to the

respiratory system, including cancer of respiratory system tissues, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting the production and function of the polypeptides of the present invention.

SUMM . . . line)

SK-

L0384 NCI_CGAP_Pr23 prostate tumor prostate pBluescript

SK-

L0438 normalized infant brain total brain brain lafmid BA

cDNA

L0439 Soares infant brain ***INIB*** whole brain Lafmid BA

L0455 Human retina cDNA retina eye lambda gt10

randomly primed

sublibrary

L0456 Human retina cDNA retina eye lambda. . .

SUMM . . . enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: Vibrio cholerae, ***Mycobacterium*** leprae, Salmonella typhi, Salmonella paratyphi, Meisseria meningitidis, Streptococcus pneumoniae, Group B streptococcus, Shigella spp., Enterotoxigenic Escherichia coli, Enterohemorrhagic E. coli,. . .

SUMM . . . Yersinia, Shigella), Erysipelothrix, Haemophilus (e.g., Haemophilus influenza type B), Helicobacter, Legionella (e.g., Legionella pneumophila), Leptospira, Listeria (e.g., Listeria monocytogenes), Mycoplasma, ***Mycobacterium*** (e.g., ***Mycobacterium*** leprae and ***Mycobacterium*** tuberculosis), Vibrio (e.g., Vibrio cholerae), Neisseriaceae (e.g., Neisseria gonorrhea, Neisseria meningitidis), Pasteurellacea, Proteus, Pseudomonas (e.g., Pseudomonas aeruginosa), Rickettsiaceae, Spirochetes (e.g.,. . .

DETD . . . the invention are used in any combination with ISONIAZID.TM., RIFAMPIN.TM., PYRAZINAMIDE.TM., and/or ETHAMBUTOL.TM. to prophylactically treat or prevent an opportunistic ***Mycobacterium*** avium complex infection. In another specific embodiment, Therapeutics of the invention are used in any combination with RIFABUTIN.TM., CLARITHROMYCIN.TM., and/or AZITHROMYCIN.TM. to prophylactically treat or prevent an opportunistic ***Mycobacterium*** tuberculosis infection. In another specific embodiment, Therapeutics of the invention are used in any combination with GANCICLOVIR.TM., FOSCARNET.TM., and/or CIDOFOVIR.TM.. . .

L11 ANSWER 9 OF 17 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 1

AN 2003:14251 BIOSIS

DN PREV200300014251

TI In situ detection of ***Mycobacterium*** tuberculosis transcripts in human lung granulomas reveals differential gene expression in necrotic lesions.

AU Fenhalls, Gael (1); Stevens, Liesel; Moses, Lorraine; Bezuidenhout, Juanita; Betts, Joanna C.; van Helden, Paul; Lukey, Pauline T.; Duncan,

Ken

CS (1) Department of Medical Biochemistry, Faculty of Health Sciences, University of Stellenbosch, Francie van Zijl Avenue, Tygerberg, 7505, South Africa: gfen@sun.ac.za South Africa

SO Infection and Immunity, (November 2002, 2002) Vol. 70, No. 11, pp. 6330-6338. print.
ISSN: 0019-9567.

DT Article

LA English

AB We have used RNA-RNA in situ hybridization to detect the expression of several ***Mycobacterium*** tuberculosis genes in tuberculous granulomas in lung tissue sections from tuberculosis patients. The M. tuberculosis genes chosen fall into two classes. Four genes (icl, narX, and Rv2557 and Rv2558) have been implicated in the persistence of the bacterium in the host, and two genes (***iniB*** and kasA) are upregulated in response to isoniazid exposure. Both necrotic and nonnecrotic granulomas were identified in all of the patients. Necrotic granulomas were divided into three zones: an outer lymphocyte cuff containing lymphocytes and macrophages, a transition zone consisting of necrotic material interspersed with macrophages, and a central acellular necrotic region. Transcripts of all of the genes studied were found in nonnecrotic granulomas and in the lymphocyte cuff of necrotic granulomas. ***Mycobacterial*** gene expression was associated with CD68-positive myeloid cells. Rv2557 and/or its homologue Rv2558, kasA, and ***iniB*** were expressed within the transition zone of necrotic granulomas, whereas icl and narX transcripts were absent from this area. There was no evidence of transcription of any of the genes examined in the central necrotic region, although ***mycobacterial*** DNA was present. The differential expression of genes within granulomas demonstrates that M. tuberculosis exists in a variety of metabolic states and may be indicative of the response to different microenvironments. These observations confirm that genes identified in models of persistence or in response to drug treatment in vitro are expressed in the human host.

TI In situ detection of ***Mycobacterium*** tuberculosis transcripts in human lung granulomas reveals differential gene expression in necrotic lesions.

AB We have used RNA-RNA in situ hybridization to detect the expression of several ***Mycobacterium*** tuberculosis genes in tuberculous granulomas in lung tissue sections from tuberculosis patients. The M. tuberculosis genes chosen fall into two. . . narX, and Rv2557 and Rv2558) have been implicated in the persistence of the bacterium in the host, and two genes (***iniB*** and kasA) are upregulated in response to isoniazid exposure. Both necrotic and nonnecrotic granulomas were identified in all of the. . . Transcripts of all of the genes studied were found in nonnecrotic granulomas and in the lymphocyte cuff of necrotic granulomas. ***Mycobacterial*** gene expression was associated with CD68-positive myeloid cells. Rv2557 and/or its homologue Rv2558, kasA, and ***iniB*** were expressed within the transition zone of necrotic granulomas, whereas icl and narX transcripts were absent from this area. There was no evidence of transcription of any of the genes examined in the central necrotic region, although ***mycobacterial*** DNA was present. The differential expression of genes within granulomas demonstrates that M. tuberculosis exists in a variety of metabolic. . .

BC ***Mycobacteriaceae*** 08881
Hominidae 86215

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia;

Mycobacteriaceae : ***Mycobacteria*** , Actinomycetes and Related Organisms, Eubacteria, Bacteria, Microorganisms

ORGN Organism Name
Mycobacterium tuberculosis (***Mycobacteriaceae***): pathogen; human (Hominidae): patient

ORGN Organism Superterms
Animals; Bacteria; Chordates; Eubacteria; Humans; Mammals; Microorganisms; Primates; Vertebrates

GEN ***Mycobacterium*** tuberculosis Rv2557 gene (***Mycobacteriaceae***): differential expression; ***Mycobacterium*** tuberculosis Rv2558 gene (***Mycobacteriaceae***): differential expression; ***Mycobacterium*** tuberculosis icl gene (***Mycobacteriaceae***): differential expression; ***Mycobacterium*** tuberculosis ***iniB*** gene (***Mycobacteriaceae***): differential expression; ***Mycobacterium*** tuberculosis kasA gene (***Mycobacteriaceae***): differential expression; ***Mycobacterium*** tuberculosis narX gene (***Mycobacteriaceae***): differential expression

L11 ANSWER 10 OF 17 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
AN 2002:613010 SCISEARCH
GA The Genuine Article (R) Number: 574VC
TI Induction of cell-mediated immunity to Staphylococcus aureus in the mouse mammary gland by local immunization with a live attenuated mutant
AU Gomez M I; Sordelli D O (Reprint); Buzzola F R; Gracia V E
CS Univ Buenos Aires, Fac Med, Dept Microbiol, Paraguay 2155 P-12, RA-1121 Buenos Aires, DF, Argentina (Reprint); Univ Buenos Aires, Fac Med, Dept Microbiol Parasitol & Immunol, RA-1121 Buenos Aires, DF, Argentina
CYA Argentina
SO INFECTION AND IMMUNITY, (AUG 2002) Vol. 70, No. 8, pp. 4254-4260. Publisher: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904 USA.
ISSN: 0019-9567.
DT Article; Journal
LA English
REC Reference Count: 38
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The efficacy of intramammary (Ima) immunization with a live attenuated (la) Staphylococcus aureus mutant to protect the mouse mammary gland from infection has previously been established. The present study was aimed at evaluating whether Ima immunization with la-S. aureus can induce cell-mediated immune responses to the pathogen within the mammary gland. Mice were immunized by Ima route with la-S. aureus, and regional lymph node mononuclear cells were obtained thereafter. A higher expression of the interleukin-2 receptor was found on B and T cells from immunized mice when they were compared with control mice. Immunization with la-S. aureus induced strong proliferative responses to S. aureus. Moreover, significantly increased levels of gamma interferon (IFN-gamma) were produced by CD4(+) T cells when lymphocytes from immunized mice, but not from control mice, were cultured in the presence of staphylococcal antigens. Moreover, a significant increase in the percentage of IFN-gamma-producing CD4(+) and CD8(+) T cells was observed after S. aureus ***Inia*** challenge in immunized mice compared to challenged control mice. Our results demonstrated that Ima immunization with la-S. aureus induced primed lymphocyte populations capable of responding against staphylococcal antigens during in vitro stimulation, as well as during in vivo infection by S. aureus. CD4(+) and CD8(+) T cells appear to be the

main lymphocyte subpopulations involved in this response. It is suggested that IFN-gamma production induced by Ima immunization may play a pivotal role in the eradication of intracellular staphylococci.

AB . . . antigens. Moreover, a significant increase in the percentage of IFN-gamma-producing CD4(+) and CD8(+) T cells was observed after S. aureus ***Inia*** challenge in immunized mice compared to challenged control mice. Our results demonstrated that Ima immunization with la-S. aureus induced primed. . .

STP KeyWords Plus (R): ***MYCOBACTERIUM*** -TUBERCULOSIS INFECTION; T-CELLS; BOVINE MASTITIS; FIELD TRIAL; INTRAMAMMARY IMMUNIZATION; PERIPARTURIENT PERIOD; EXPERIMENTAL VACCINE; INTERFERON-GAMMA; COW MILK; INTERNALIZATION

L11 ANSWER 11 OF 17 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

AN 2002:253812 SCISEARCH

GA The Genuine Article (R) Number: 531RC

TI Distinct protein patterns associated with Listeria monocytogenes ***InIA*** - or ***InIB*** -phagosomes

AU Pizzaro-Cerda J; Jonquieres R; Gouin E; Vandekerckhove J; Garin J; Cossart P (Reprint)

CS Inst Pasteur, Unite Interact Bacteries Cellules, F-75724 Paris, France (Reprint); State Univ Ghent, Fac Med, Dept Biochem, B-9000 Ghent, Belgium; CEA, Lab Chim Prot, F-38054 Grenoble, France

CYA France; Belgium

SO CELLULAR MICROBIOLOGY, (FEB 2002) Vol. 4, No. 2, pp. 101-115.
Publisher: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND.
ISSN: 1462-5814.

DT Article; Journal

LA English

REC Reference Count: 47

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Internalization of Listeria monocytogenes into non-phagocytic cells is mediated by the interactions between the two bacterial invasion proteins ***InIA*** (internalin) and ***InIB*** and their cellular surface receptors E-cadherin and c-Met. To get an insight into all the cellular components necessary for uptake and early intracellular life, we undertook a global proteomic characterization of the early listerial phagosome in the human epithelial cell line LoVo. First, we proceeded to an immunocytochemical characterization of intracellular marker recruitment to phagosomes containing latex beads coated with ***InIA*** or ***InIB*** . E-cadherin and c-Met were, as expected, rapidly recruited to the phagosomal formation site. Phagosomes subsequently acquired the early endosomal antigen 1 (EEA1) and the lysosomal-associated membrane protein 1 (LAMP1), while presenting a more delayed enrichment of the lysosomal hydrolase cathepsin D. Early phagosomes devoid of lysosomal, endoplasmic reticulum and Golgi enzymatic activities could then be isolated by subcellular fractionation of LoVo cells. Two-dimensional gel electrophoresis (2DPAGE) revealed differences between the protein profiles of ***InIA*** - or ***InIB*** -phagosomes and those of early/late endosomes or lysosomes of naive LoVo cells. One major protein specifically recruited on the ***InIB*** -phagosomes was identified by mass spectrometry as MSF, a previously reported member of the septin family of GTPases. MSF forms filaments that co-localize with the actin cytoskeleton in resting cells and it is recruited to the entry site of ***InIB*** -coated beads. These results suggest that MSF is a putative effector of

the ***InIB*** -mediated internalization of L. monocytogenes into host cells.

TI Distinct protein patterns associated with Listeria monocytogenes ***InIA*** - or ***InIB*** -phagosomes

AB Internalization of Listeria monocytogenes into non-phagocytic cells is mediated by the interactions between the two bacterial invasion proteins ***InIA*** (internalin) and ***InIB*** and their cellular surface receptors E-cadherin and c-Met. To get an insight into all the cellular components necessary for uptake. . . line LoVo. First, we proceeded to an immunocytochemical characterization of intracellular marker recruitment to phagosomes containing latex beads coated with ***InIA*** or ***InIB*** . E-cadherin and c-Met were, as expected, rapidly recruited to the phagosomal formation site. Phagosomes subsequently acquired the early endosomal antigen. . . then be isolated by subcellular fractionation of LoVo cells. Two-dimensional gel electrophoresis (2DPAGE) revealed differences between the protein profiles of ***InIA*** - or ***InIB*** -phagosomes and those of early/late endosomes or lysosomes of naive LoVo cells. One major protein specifically recruited on the ***InIB*** -phagosomes was identified by mass spectrometry as MSF, a previously reported member of the septin family of GTPases. MSF forms filaments that co-localize with the actin cytoskeleton in resting cells and it is recruited to the entry site of ***InIB*** -coated beads. These results suggest that MSF is a putative effector of the ***InIB*** -mediated internalization of L. monocytogenes into host cells.

STP KeyWords Plus (R): ACUTE MYELOID-LEUKEMIA; RICH REPEAT REGION; E-CADHERIN; PHOSPHOINOSITIDE 3-KINASE; ***MYCOBACTERIAL*** PHAGOSOME; ENDOSOMAL LOCALIZATION; INVASION PROTEIN; EPITHELIAL-CELLS; MAMMALIAN-CELLS; SURFACE PROTEIN

L11 ANSWER 12 OF 17 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 2

AN 2001:455186 BIOSIS

DN PREV200100455186

TI ***IniB*** , ***iniA*** and ***iniC*** genes of ***mycobacteria*** and methods of use.

AU Alland, David; Bloom, Barry R.; Jacobs, William R., Jr.

CS Dobbs Ferry, NY USA
ASSIGNEE: Albert Einstein College of Medicine of Yeshiva University

PI US 6268201 July 31, 2001

SO Official Gazette of the United States Patent and Trademark Office Patents, (July 31, 2001) Vol. 1248, No. 5, pp. No Pagination. e-file.
ISSN: 0098-1133.

DT Patent

LA English

AB This invention relates to the identification, cloning, sequencing and characterization of the ***iniB*** , ***iniA*** and ***iniC*** genes of ***mycobacteria*** which are induced by a broad class of antibiotics that act by inhibiting cell wall biosynthesis, including the first line antituberculosis agents, isoniazid and ethambutol. The present invention provides purified and isolated ***iniB*** , ***iniA*** , ***iniC*** and ***iniB*** promoter nucleic acids which may comprise the iniBAC operon, as well as mutated forms of these nucleic acids. The present invention also provides one or more single-stranded nucleic acid probes which specifically hybridize to the ***iniB*** , ***iniA*** , ***iniC*** and ***iniB*** promoter nucleic acids, and mixtures thereof, which may be formulated in kits, and used in the diagnosis of

drug-resistant ***mycobacterial*** strain. The present invention also provides methods for the screening and identification of drugs effective against ***Mycobacterium*** tuberculosis using induction of the ***iniB*** promoter.

TI ***IniB*** , ***iniA*** and ***iniC*** genes of ***mycobacteria*** and methods of use.

AB This invention relates to the identification, cloning, sequencing and characterization of the ***iniB*** , ***iniA*** and ***iniC*** genes of ***mycobacteria*** which are induced by a broad class of antibiotics that act by inhibiting cell wall biosynthesis, including the first line antituberculosis agents, isoniazid and ethambutol. The present invention provides purified and isolated ***iniB*** , ***iniA*** , ***iniC*** and ***iniB*** promoter nucleic acids which may comprise the iniBAC operon, as well as mutated forms of these nucleic acids. The present invention also provides one or more single-stranded nucleic acid probes which specifically hybridize to the ***iniB*** , ***iniA*** , ***iniC*** and ***iniB*** promoter nucleic acids, and mixtures thereof, which may be formulated in kits, and used in the diagnosis of drug-resistant ***mycobacterial*** strain. The present invention also provides methods for the screening and identification of drugs effective against ***Mycobacterium*** tuberculosis using induction of the ***iniB*** promoter.

BC ***Mycobacteriaceae*** 08881

IT Methods & Equipment
mycobacterial gene utilization method: genetic method

GEN ***mycobacteria*** ***iniA*** gene (***Mycobacteriaceae***);
mycobacteria ***iniB*** gene (***Mycobacteriaceae***);
mycobacteria ***iniC*** gene (***Mycobacteriaceae***)

L11 ANSWER 13 OF 17 USPATFULL on STN

AN 2001:223877 USPATFULL

TI METHOD OF IDENTIFICATION OF DIFFERENTIALLY EXPRESSED MRNA

IN ALLAND, DAVID, DOBBS FERRY, NY, United States
BLOOM, BARRY R., CAMBRIDGE, MA, United States
KRAMNIK, IGOR, BRONX, NY, United States

PI US 2001049094 A1 20011206
US 6458566 B2 20021001

AI US 1998-178098 A1 19981023 (9)

DT Utility

FS APPLICATION

LREP CRAIG J ARNOLD, AMSTER ROTHSTEIN & EBENSTEIN, 90 PARK AVENUE, NEW YORK, NY, 10016

CLMN Number of Claims: 30

ECL Exemplary Claim: 1

DRWN 8 Drawing Page(s)

LN.CNT 1036

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The method provided by the present invention sets forth a novel combination of methods and principles which allows for the rapid and accurate isolation and identification of a large number of differentially expressed mRNAs.

SUMM . . . to environmental stimuli can provide valuable insights into cellular mechanisms (1-5). This approach is particularly well suited for studies of ***Mycobacterium*** tuberculosis, a pathogen that must adapt to a variety of hostile milieu including phagocytosis by macrophages and treatment with antibiotics.. . .

DRWD [0006] FIG. 3: FIG. 3 shows the results of Induction of ***iniA***

after treatment with different antibiotics. Autoradiographs of a Northern blot containing RNA from M. tuberculosis cultures treated either with no. . . isoniazid 1 .mu.g/ml; ethambutol 5 .mu.g/ml; streptomycin 5 .mu.g/ml; and rifampin 5 .mu.g/ml. The blots were hybridized first with an ***iniA*** DNA probe (top) to examine ***iniA*** induction; the blot was then stripped and re-hybridized with a 16S probe (bottom) to confirm equal RNA loading.

DRWD . . . was equalized by comparison of the 23S band intensity. RT PCR using three ten-fold dilutions of each RNA and either ***iniA*** , asd or 16S specific primers was performed. Induction of ***iniA*** and suppression of asd by isoniazid is demonstrated. The amount of 16S RT PCR product is similar for equivalent dilutions,. . . RNA. Lanes 7-8 are minus RT controls; and lane 9 a negative PCR control. FIG. 4B sets forth lack of ***iniA*** induction in an isoniazid resistant strain. Cultures of isogenic BCG strain ATCC35735 which is susceptible to isoniazid (lanes 1-6), or. . . for the last 18 hours. Three ten-fold dilutions of RNA extracted from each culture were tested by RT PCR for ***iniA*** induction. Induction is seen only in the INH susceptible strain. Lanes 13-16 are minus RT controls; and lane 17 a. . .

DETD . . . be obtained from bacteria. In a preferred embodiment of the invention, the cDNA, RNA or genomic DNA is obtained from ***mycobacteria*** . The nucleic acid sequences of interest may be, for example, coding sequences, sequences corresponding to a particular class of genes. . .

DETD . . . be obtained from bacteria. In a preferred embodiment of the invention, the cDNA, RNA or genomic DNA is obtained from ***mycobacteria*** . The nucleic acid sequences of interest may be, for example, coding sequences, sequences corresponding to a particular class of genes. . .

DETD . . . be obtained from bacteria. In a preferred embodiment of the invention, the cDNA, RNA or genomic DNA is obtained from ***mycobacteria*** . The nucleic acid sequences of interest may be, for example, coding sequences, sequences corresponding to a particular class of genes. . .

DETD [0035] ***Mycobacterial*** cultures were grown to mid Log phase in Middlebrook 7H9 media supplemented with OADC, 0.05% Tween 80, and cyclohexamide (18). . .

DETD . . . One microgram of RNA was reverse transcribed using the appropriate reverse PCR primer and superscript II at 50.degree. C. For ***iniA*** and asd, three serial ten-fold dilutions of cDNA were made; 16S cDNA was diluted 1 in 10.sup.6, 1 in 10.sup.7,. . . with Taq polymerase and 1.times.PCR buffer (Gibco BRL) containing 2 mM MgCl.sub.2 for 25 cycles annealing at 60.degree. C. for ***iniA*** ; 35 cycles annealing at 58.degree. C. for asd; 25 cycles annealing at 63.degree. C. for 16S. PCR products were analyzed. . . the amounts of PCR product were calculated by densitometry (Imaging Software, National Institute of Health, Bethesda, Md.). Primers used for ***iniA*** : 5'-GCGCTGGCGGGAGATCGTCAATG-3', 5'-TGCGCAGTCGGGTCACAGGAGTCG-3'; for asd: 5'-TCCCGCCGCCGAACACCTA-3', 5'-GGATCCGGCCGACCAGAGA-3'; for 16S: 5'-GGAGTACGGCCGCAAGGCTAAAAC-3', 5'-CAGACCCCGATCCGAACTGAGACC-3'.

DETD . . . frame that appeared to be the second gene of a probable three gene operon. This open reading frame was named ***iniA*** (isoniazid

induced gene A), and the upstream open reading frame Rv0341, was named ***iniB*** . P2 encoded a sequence that was not complementary to P1, but that was identical to the third gene in the same probable operon Rv0343, this open reading frame was named ***iniC*** . A putative protein encoded by the ***iniA*** gene was found to contain a phosphopantetheine attachment site motif (21) suggesting that it functions as an acyl carrier protein. Both ***iniA*** and ***iniC*** lacked significant homology to other known genes but were 34% identical to each other. A sequence similarity search demonstrated that ***iniB*** had weak homology to alanineglycine rich cell wall structural proteins (22). Northern blot analysis using excised inserts to probe total RNA from M. tuberculosis cultured in the presence or absence or different antibiotics verified that ***iniA*** was strongly induced by isoniazid and ethambutol, drugs that act by inhibiting cell wall biosynthesis but not by rifampin or. . .

DETD [0066] Reverse transcription (RT) PCR assays confirmed differential gene expression of both asd and ***iniA*** (FIG. 4A), as well as of ***iniB*** and ***iniC*** (data not shown). As predicted, ***iniA*** was strongly induced by isoniazid (70 fold induction by densitometry), while asd was repressed (17 fold). Induction of ***iniA*** was also tested in two isogenic strains of BCG that were either sensitive or resistant to isoniazid. The resistant phenotype. . . conferred by a mutation in katG which normally converts isoniazid from a prodrug to its active form (23). Induction of ***iniA*** was seen only in the susceptible BCG strain demonstrating the requirement for isoniazid activation (FIG. 4B).

DETD . . . active antibiotics that have different mechanisms of action (23, 25-28) adds further complexity to this issue. The role of the ***iniA*** operon is not well understood. The phosphopantetheine attachment site motif encoded by the ***iniA*** gene suggests that it encodes an acyl carrier protein, however it may also have other functions. Another acyl carrier protein. . . acpM has been described recently that both binds to and is induced by isoniazid (26). However no gene in the ***iniA*** operon has significant homology to any gene in the operon containing acpM or to the antigen 85 complex that has also been shown to be induced by isoniazid (29). Unlike these genes, only ***iniA*** is induced by both isoniazid and ethambutol. The inventors speculate that the ***iniA*** operon may be induced as a protective response to cell wall mediated cellular injury. If this is the case, agents capable of blocking ***iniA*** , ***iniB*** , or ***iniC*** function would be expected to act synergistically with isoniazid and other cell wall active antibiotics to kill M. tuberculosis.

L11 ANSWER 14 OF 17 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 3
AN 2000:179354 BIOSIS
DN PREV200000179354
TI Characterization of the ***Mycobacterium*** tuberculosis iniBAC promoter, a promoter that responds to cell wall biosynthesis inhibition.
AU Alland, David (1); Steyn, Andries J.; Weisbrod, Torin; Aldrich, Kate; Jacobs, William R., Jr.
CS (1) Division of Infectious Diseases, Montefiore Medical Center, 111 East 210th St., Centennial Building 4th floor, Bronx, NY, 10467 USA
SO Journal of Bacteriology, (April, 2000) Vol. 182, No. 7, pp. 1802-1811. ISSN: 0021-9193.
DT Article

LA English
SL English
AB The cell wall provides an attractive target for antibiotics against ***Mycobacterium*** tuberculosis. Agents such as isoniazid and ethambutol that work by inhibiting cell wall biosynthesis are among the most highly effective antibiotics against this pathogen. Although considerable progress has been made identifying the targets for cell wall active antibiotics, little is known about the intracellular mechanisms that are activated as a consequence of cell wall injury. These mechanisms are likely to have an important role in growth regulation and in the induction of cell death by antibiotics. We previously discovered three isoniazid-induced genes (***iniB*** , ***iniA*** , and ***iniC***) organized in tandem on the M. tuberculosis genome. Here, we investigate the unique features of the putative iniBAC promoter. This promoter was specifically induced by a broad range of inhibitors of cell wall biosynthesis but was not inducible by other conditions that are toxic to ***mycobacteria*** via other mechanisms. Induction required inhibitory concentrations of antibiotics and could be detected only in actively growing cells. Analysis of the iniBAC promoter sequence revealed both a regulatory element upstream and a potential repressor binding region downstream of the transcriptional start site. The induction phenotype and structure of the iniBAC promoter suggest that a complex intracellular response occurs when cell wall biosynthesis is inhibited in M. tuberculosis and other ***mycobacteria*** .
TI Characterization of the ***Mycobacterium*** tuberculosis iniBAC promoter, a promoter that responds to cell wall biosynthesis inhibition.
AB The cell wall provides an attractive target for antibiotics against ***Mycobacterium*** tuberculosis. Agents such as isoniazid and ethambutol that work by inhibiting cell wall biosynthesis are among the most highly effective. . . important role in growth regulation and in the induction of cell death by antibiotics. We previously discovered three isoniazid-induced genes (***iniB*** , ***iniA*** , and ***iniC***) organized in tandem on the M. tuberculosis genome. Here, we investigate the unique features of the putative iniBAC promoter. This. . . a broad range of inhibitors of cell wall biosynthesis but was not inducible by other conditions that are toxic to ***mycobacteria*** via other mechanisms. Induction required inhibitory concentrations of antibiotics and could be detected only in actively growing cells. Analysis of. . . iniBAC promoter suggest that a complex intracellular response occurs when cell wall biosynthesis is inhibited in M. tuberculosis and other ***mycobacteria*** .
BC ***Mycobacteriaceae*** 08881
ORGN Super Taxa
Mycobacteriaceae : ***Mycobacteria*** , Actinomycetes and Related Organisms, Eubacteria, Bacteria, Microorganisms
ORGN Organism Name
Mycobacterium tuberculosis (***Mycobacteriaceae***); ***mycobacteria*** (***Mycobacteriaceae***)
ORGN Organism Superterms
Bacteria; Eubacteria; Microorganisms

L11 ANSWER 15 OF 17 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 4
AN 2000:119676 BIOSIS
DN PREV200000119676
TI Molecular genetic analysis of nucleotide polymorphisms associated with ethambutol resistance in human isolates of ***Mycobacterium***

tuberculosis.

AU Ramaswamy, Srinivas V.; Amin, Amol G.; Goksel, Servet; Stager, Charles E.; Dou, Shu-Jun; El Sahly, Hana; Moghazeh, Soraya L.; Kreiswirth, Barry N.; Musser, James M. (1)

CS (1) Laboratory of Human Bacterial Pathogenesis, Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 903 S. 4th St., Hamilton, MT, 59840 USA

SO Antimicrobial Agents and Chemotherapy, (Feb., 2000) Vol. 44, No. 2, pp. 326-336.
ISSN: 0066-4804.

DT Article

LA English

SL English

AB Ethambutol (EMB) is a central component of drug regimens used worldwide for the treatment of tuberculosis. To gain insight into the molecular genetic basis of EMB resistance, approximately 2 Mb of five chromosomal regions with 12 genes in 75 epidemiologically unassociated EMB-resistant and 33 EMB-susceptible ***Mycobacterium*** tuberculosis strains isolated from human patients were sequenced. Seventy-six percent of EMB-resistant organisms had an amino acid replacement or other molecular change not found in EMB-susceptible strains. Thirty-eight (51%) EMB-resistant isolates had a resistance-associated mutation in only 1 of the 12 genes sequenced. Nineteen EMB-resistant isolates had resistance-associated nucleotide changes that conferred amino acid replacements or upstream potential regulatory region mutations in wo or more genes. Most isolates (68%) with resistance-associatedmutations in a single gene had nucleotide changes in embB, a gene encoding an arabinosyltransferase involved in cell wall biosynthesis. The majority of these mutations resulted in amino acid replacements at position 306 or 406 of EmbB. Resistance-associated mutations were also identified in several genes recently shown to be upregulated in response to exposure of M. tuberculosis to EMB in vitro, including genes in the ***iniA*** operon. Approximately one-fourth of the organisms studied lacked mutations inferred to participate in EMB resistance, a result indicating that one or more genes that mediate resistance to this drug remain to be discovered. Taken together, the results indicate that there are multiple molecular pathways to the EMB resistance phenotype.

TI Molecular genetic analysis of nucleotide polymorphisms associated with ethambutol resistance in human isolates of ***Mycobacterium*** tuberculosis.

AB. . . EMB resistance, approximately 2 Mb of five chromosomal regions with 12 genes in 75 epidemiologically unassociated EMB-resistant and 33 EMB-susceptible ***Mycobacterium*** tuberculosis strains isolated from human patients were sequenced. Seventy-six percent of EMB-resistant organisms had an amino acid replacement or other. . . recently shown to be upregulated in response to exposure of M. tuberculosis to EMB in vitro, including genes in the ***iniA*** operon. Approximately one-fourth of the organisms studied lacked mutations inferred to participate in EMB resistance, a result indicating that one. . .

BC ***Mycobacteriaceae*** 08881
Hominidae 86215

IT Major Concepts
Molecular Genetics (Biochemistry and Molecular Biophysics); Pharmacology

IT Chemicals & Biochemicals
ethambutol; ***iniA*** operon; ***Mycobacterium*** tuberculosis embA gene (***Mycobacteriaceae***); ***Mycobacterium***

tuberculosis embB gene (***Mycobacteriaceae***); ***Mycobacterium*** tuberculosis embC gene (***Mycobacteriaceae***); ***Mycobacterium*** tuberculosis embR gene (***Mycobacteriaceae***); ***Mycobacterium*** tuberculosis rmlD gene (***Mycobacteriaceae***)

ORGN Super Taxa

Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; ***Mycobacteriaceae*** : ***Mycobacteria*** , Actinomycetes and Related Organisms, Eubacteria, Bacteria, Microorganisms

ORGN Organism Name

Mycobacterium avium (***Mycobacteriaceae***); ***Mycobacterium*** leprae (***Mycobacteriaceae***); ***Mycobacterium*** smegmatis (***Mycobacteriaceae***); ***Mycobacterium*** tuberculosis (***Mycobacteriaceae***); human (Hominidae)

ORGN Organism Superterms

Animals; Bacteria; Chordates; Eubacteria; Humans; Mammals; Microorganisms; Primates; Vertebrates

L11 ANSWER 16 OF 17 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

AN 2000:378898 BIOSIS

DN PREV200000378898

TI Identification and characterization of a ***Mycobacterium*** tuberculosis promoter that is induced by a broad range of antibiotics that inhibit cell wall biosynthesis.

AU Alland, David (1); Cerny, Rosaria (1); Steyn, Adrie J.; Weisbrod, Torin; Bloom, Barry R.; Jacobs, William R., Jr.

CS (1) Division of Infectious Diseases, Montefiore Medical Center, Bronx, NY, 10467 USA

SO Tubercle and Lung Disease, (2000) Vol. 80, No. 2, pp. 85-86. print.
Meeting Info.: Tuberculosis-Leprosy Panel's 34th Annual Research Conference on the US-Japan Cooperative Medical Science Program San Francisco, California, USA June 27-30, 1999
ISSN: 0962-8479.

DT Conference

LA English

SL English

TI Identification and characterization of a ***Mycobacterium*** tuberculosis promoter that is induced by a broad range of antibiotics that inhibit cell wall biosynthesis.

BC ***Mycobacteriaceae*** 08881

IT Major Concepts

Membranes (Cell Biology); Infection; Pharmacology

IT Chemicals & Biochemicals

ethambutol: antibacterial - drug; isoniazid: antibacterial - drug; ***Mycobacterium*** tuberculosis ***iniA*** gene (***Mycobacteriaceae***); ***Mycobacterium*** tuberculosis ***iniB*** gene (***Mycobacteriaceae***); ***Mycobacterium*** tuberculosis ***iniC*** gene (***Mycobacteriaceae***)

ORGN Super Taxa

Mycobacteriaceae : ***Mycobacteria*** , Actinomycetes and Related Organisms, Eubacteria, Bacteria, Microorganisms

ORGN Organism Name

Mycobacterium tuberculosis (***Mycobacteriaceae***)

ORGN Organism Superterms

Bacteria; Eubacteria; Microorganisms

L11 ANSWER 17 OF 17 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 5
AN 1999:4927 BIOSIS
DN PREV199900004927
TI Identification of differentially expressed mRNA in prokaryotic organisms by customized amplification libraries (DECAL): The effect of isoniazid on gene expression in ***Mycobacterium*** tuberculosis.
AU Alland, David (1); Kramnik, Igor; Weisbrod, Torin R.; Otsubo, Lisa; Cerny, Rosaria; Miller, Lincoln P.; Jacobs, William R., Jr.; Bloom, Barry R.
CS (1) Div. Infectious Disease, Montefiore Medical Cent., 111 East 210th St., Bronx, NY 10467 USA
SO Proceedings of the National Academy of Sciences of the United States of America, (Oct. 27, 1998) Vol. 95, No. 22, pp. 13227-13232.
ISSN: 0027-8424.
DT Article
LA English
AB Understanding the effects of the external environment on bacterial gene expression can provide valuable insights into an array of cellular mechanisms including pathogenesis, drug resistance, and, in the case of ***Mycobacterium*** tuberculosis, latency. Because of the absence of poly(A)+ mRNA in prokaryotic organisms, studies of differential gene expression currently must be performed either with large amounts of total RNA or rely on amplification techniques that can alter the proportional representation of individual mRNA sequences. We have developed an approach to study differences in bacterial mRNA expression that enables amplification by the PCR of a complex mixture of cDNA sequences in a reproducible manner that obviates the confounding effects of selected highly expressed sequences, e.g., ribosomal RNA. Differential expression using customized amplification libraries (DECAL) uses a library of amplifiable genomic sequences to convert total cellular RNA into an amplified probe for gene expression screens. DECAL can detect 4-fold differences in the mRNA levels of rare sequences and can be performed on as little as 10 ng of total RNA. DECAL was used to investigate the in vitro effect of the antibiotic isoniazid on M. tuberculosis, and three previously uncharacterized isoniazid-induced genes, ***iniA*** , ***iniB*** , and ***iniC*** , were identified. The ***iniB*** gene has homology to cell wall proteins, and ***iniA*** contains a phosphopantetheine attachment site motif suggestive of an acyl carrier protein. The ***iniA*** gene is also induced by the antibiotic ethambutol, an agent that inhibits cell wall biosynthesis by a mechanism that is distinct from isoniazid. The DECAL method offers a powerful new tool for the study of differential gene expression.
TI . . of differentially expressed mRNA in prokaryotic organisms by customized amplification libraries (DECAL): The effect of isoniazid on gene expression in ***Mycobacterium*** tuberculosis.
AB . . expression can provide valuable insights into an array of cellular mechanisms including pathogenesis, drug resistance, and, in the case of ***Mycobacterium*** tuberculosis, latency. Because of the absence of poly(A)+ mRNA in prokaryotic organisms, studies of differential gene expression currently must be. . . used to investigate the in vitro effect of the antibiotic isoniazid on M. tuberculosis, and three previously uncharacterized isoniazid-induced genes, ***iniA*** , ***iniB*** , and ***iniC*** , were identified. The ***iniB*** gene has homology to cell wall proteins, and ***iniA*** contains a phosphopantetheine attachment site motif suggestive of an acyl carrier

protein. The ***iniA*** gene is also induced by the antibiotic ethambutol, an agent that inhibits cell wall biosynthesis by a mechanism that is. . .

BC ***Mycobacteriaceae*** 08881

IT . . .
(Biochemistry and Molecular Biophysics)

IT Chemicals & Biochemicals
ethambutol: antibacterial - drug; isoniazid: antibacterial - drug; mRNA [messenger RNA]: expression; ***Mycobacterium*** tuberculosis ***iniA*** gene (***Mycobacteriaceae***): expression; ***Mycobacterium*** tuberculosis ***iniB*** gene (***Mycobacteriaceae***): expression; ***Mycobacterium*** tuberculosis ***iniC*** gene (***Mycobacteriaceae***): expression

ORGN Super Taxa
Mycobacteriaceae : ***Mycobacteria*** , Actinomycetes and Related Organisms, Eubacteria, Bacteria, Microorganisms

ORGN Organism Name
Mycobacterium -tuberculosis (***Mycobacteriaceae***)

ORGN Organism Superterms
Bacteria; Eubacteria; Microorganisms

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STN INTERNATIONAL LOGOFF AT 08:00:48 ON 25 AUG 2003